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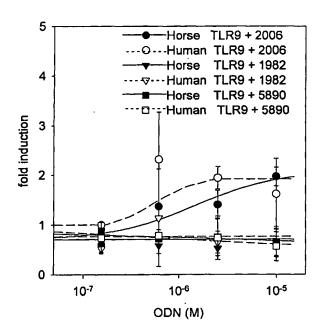
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(54) Title: TOLL-LIKE RECEPTOR 9 (TLR9) FROM VARIOUS MAMMALIAN SPECIES



(57) Abstract: Novel amino acid and nucleotide sequences for rat, pig (porcine), cow (bovine), horse (equine), and sheep (ovine) Toll-like receptor 9 (TLR9) are provided. Also provided are amino acid and nucleotide sequences for dog (canine), cat (feline), mouse (murine), and human TLR9. Comparison of these sequences, especially in combination with functional assessment for species-specific CpG motif preferences, permits identification of specific regions and amino acid residues of interest in TLR9 ligand interaction. Novel chimeric TLR9 receptor molecules, cells expressing these molecules, and methods for their use in screening assays for TLR9 ligands are also provided.



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TOLL-LIKE RECEPTOR 9 (TLR9) FROM VARIOUS MAMMALIAN SPECIES

Background of the Invention

Synthetic oligodeoxynucleotides (ODN) and DNA containing immunostimulatory CpG motifs (CpG DNA) function as potent adjuvants and activators of the innate immune system. Heeg K et al. (2000) *Int Arch Allergy Immunol* 121:87-97; Krieg AM (2001) *Vaccine* 19:618-22. A wide variety of CpG-containing sequences have been screened for biological activity and it is reported that optimal CpG DNA sequences can vary among species. Rankin R et al. (2001) *Antisense Nucleic Acid Drug Dev* 11:333-40.

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Toll-like receptor 9 (TLR9) has recently been identified as a receptor for CpG ODN. Hemmi H et al. (2000) *Nature* 408:740-5. The molecular mechanism by which TLR9 recognizes CpG DNA is not understood.

Summary of the Invention

Toll-like receptor 9 (TLR9) is known to be involved in innate immunity and to signal in response to CpG DNA. To date, the amino acid sequences only of human and murine TLR9 have been reported, and, interestingly, these two species are known to prefer different CpG motifs. The structural basis for this species-specific CpG motif preference has not yet been fully elucidated. The instant invention provides, in part, novel amino acid and nucleotide sequences of rat, pig, cow, and horse TLR9. These novel TLR9 sequences are useful for elucidating certain key structural features of TLR9. Specifically, comparison of sequences of murine, human, and these novel TLR9 sequences permits identification of areas of highly conserved sequence, areas of group conservation, and areas of hypervariability. In addition, such comparisons permit an assessment of evolutionary relatedness among TLR9 molecules of the various species, as well as an assessment of inter-species homologies. Importantly, such comparisons permit a rational basis for identifying amino acids in TLR9 that may be involved in the CpG binding site, as well as amino acids involved in conferring species specificity for particular CpG motifs. Such information may be used to design and construct novel TLR9 molecules which incorporate specific point or regional mutations and which possess desired ligand binding characteristics. Such information may also be useful in designing and identifying novel ligands for TLR9 of a given species.

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In one aspect, the invention provides isolated polypeptides having amino acid sequences for rat, pig (porcine), cow (bovine), horse (equine), and sheep (ovine) TLR9 polypeptides. These amino acid sequences correspond to SEQ ID NOs 1, 5, 9, 13, and 17, respectively. Each of these sequences is believed to include at least a majority of an extracellular domain, as well as a transmembrane region and at least part of a TLR/IL-1 receptor (TIR) domain. To the extent any such sequence may lack an amino-terminal and/or carboxy-terminal sequence, such sequence is ascertainable, without undue experimentation, using conventional molecular biology techniques and the sequence information provided herein.

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In another aspect the invention provides isolated polypeptides having amino acid sequences for essentially the whole extracellular domain, optionally including a signal peptide, of each of rat, porcine, bovine, equine, and ovine TLR9. These amino acid sequences correspond to SEQ ID NOs 2, 6, 10, 14, and 18, respectively. Such extracellular domains are believed to include sequence specifically involved in binding to TLR9 ligand, such as CpG DNA. In addition, such extracellular domains are believed to include sequence that confers species specificity for particular CpG motifs.

Isolated nucleic acid molecules encoding the polypeptides just described above are also provided according to further aspects of the invention. Such nucleic acid molecules include, but are not limited to, nucleic acid molecules having sequences provided by SEQ ID NOs 3, 7, 11, 15, 19; and 4, 8, 12, 16, and 20, respectively. Isolated nucleic acid molecules encoding the TLR9 polypeptides of SEQ ID NOs 1, 5, 9, 13, 17; and 2, 6, 10, 14, and 18 also include nucleic acid molecules that differ in sequence from SEQ ID NOs 3, 7, 11, 15, 19; and 4, 8, 12, 16, and 20, respectively, due to degeneracy of the genetic code. Such nucleic acid molecules will hybridize, under stringent conditions, with suitably selected nucleic acid molecules having sequences selected from SEQ ID NOs 3, 4, 7, 8, 11, 12, 15, 16, 19, and 20.

In another aspect the invention provides a vector which includes an isolated nucleic acid molecule of the invention. In one embodiment the vector is an expression vector and the isolated nucleic acid molecule of the invention is operably linked to a regulatory sequence in the vector. When present within a cell, an expression vector according to this aspect of the invention causes the cell to express a polypeptide of the invention.

The invention according to another aspect provides a cell in which a vector of the invention is present. In one embodiment the cell containing the vector expresses a

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polypeptide of the invention. In certain embodiments the cell also contains a reporter construct that transduces a TLR9-mediated signal in response to contact of the polypeptide of the invention or a TLR9 with a suitable TLR9 ligand. The cell containing the vector, and optionally containing the reporter construct, can be used in screening methods also provided by the invention.

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In yet another aspect the invention provides an antibody or antibody fragment that binds specifically to an isolated polypeptide of the invention. In certain embodiments the antibody or antibody fragment binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide. More specifically, the antibody or antibody fragment binds uniquely to one of the isolated polypeptides of the invention. In one embodiment the antibody or antibody fragment that binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide also binds to either mouse or human TLR9. In another embodiment the antibody or antibody fragment that binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide does not also bind to either mouse or human TLR9. In some embodiments the antibody or antibody fragment binds selectively to a chimeric TLR9 polypeptide of the invention. In certain embodiments the antibody or antibody fragment of the invention is a monoclonal antibody or fragment of a monoclonal antibody.

In one aspect the invention provides a method for identifying key amino acids in a TLR9 of a first species which confer specificity for CpG DNA optimized for TLR9 of the first species. The method involves aligning protein sequences of TLR9 of a first species, TLR9 of a second species, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for TLR9 of the first species rather than when contacted with a CpG DNA optimized for TLR9 of the second species; generating an initial set of candidate amino acids in the TLR9 of the first species by excluding each amino acid in the TLR9 of the first species which (a) is identical with the TLR9 of the second species or (b) differs from the TLR9 of the second species only by conservative amino acid substitution; generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in the TLR9 of the first species which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and identifying as key amino acids in the TLR9 of the first species each amino acid in the refined set of candidate amino acids.

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In another aspect the invention provides a method for identifying key amino acids in human TLR9 which confer specificity for CpG DNA optimized for human TLR9. The method according to this aspect of the invention involves aligning protein sequences of human TLR9, murine TLR9, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for human TLR9 rather than when contacted with a CpG DNA optimized for murine TLR9; generating an initial set of candidate amino acids in human TLR9 by excluding each amino acid in human TLR9 which (a) is identical with murine TLR9 or (b) differs from murine TLR9 only by conservative amino acid substitution; generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in human TLR9 which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and identifying as key amino acids in human TLR9 each amino acid in the refined set of candidate amino acids. In one embodiment the method according to this aspect of the invention is performed iteratively with a plurality of TLR9s derived from different species other than human and mouse, wherein for each TLR9 the refined set of candidate amino acids is assigned a weight corresponding to a ratio equal to (responsiveness to human-preferred CpG DNA)/(responsiveness to murine-preferred CpG DNA).

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In another aspect the invention also provides an isolated polypeptide having an amino acid sequence identical to SEQ ID NO:30 (extracellular domain (ECD) of murine TLR9) except for substitution of at least one key amino acid identified according to the method above. The polypeptide according to this aspect of the invention is a chimeric TLR9 polypeptide. Preferably the polypeptide according to this aspect of the invention binds to CpG DNA optimized for human TLR9 better than does the isolated polypeptide having an amino acid sequence identical to SEQ ID NO:30 (ECD of murine TLR9). In one embodiment the polypeptide includes only one substituted amino acid. The isolated polypeptide according to this aspect of the invention may further include sequence involved in TLR/IL-1R signal transduction, e.g., intracellular domain of TLR9 as provided in SEQ ID NOs 29 and 33. For example, in one embodiment a polypeptide according to this aspect of the invention is an isolated polypeptide having an amino acid sequence identical to SEQ ID NO:29 (full length murine TLR9) except for substitution of at least one key amino acid identified according to the method above.

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In another aspect the invention provides an isolated nucleic acid molecule including a nucleic acid sequence encoding a chimeric TLR9 polypeptide just described. In one embodiment the isolated nucleic acid molecule has a nucleic acid sequence encoding a chimeric TLR9 polypeptide just described.

In yet another aspect, the invention provides a screening method to identify a TLR9 ligand. The method involves contacting a polypeptide (including a chimeric TLR9 polypeptide) of the invention with a candidate TLR9 ligand; measuring a signal in response to the contacting; and identifying the candidate TLR9 ligand as a TLR9 ligand when the signal in response to the contacting is consistent with TLR9 signaling. In one embodiment the candidate TLR9 ligand is an immunostimulatory nucleic acid. In one embodiment the candidate TLR9 ligand is a CpG DNA.

The invention also provides, in yet a further aspect, a screening method to identify species-specific CpG-motif preference of an isolated polypeptide of the invention. The method according to this aspect of the invention involves contacting an isolated polypeptide of the invention with a CpG DNA including a hexamer sequence selected from the group consisting of GACGTT, AACGTT, CACGTT, TACGTT, GGCGTT, GCCGTT, GTCGTT, GATGTT, GAAGTT, GAGGTT, GACATT, GACCTT, GACTTT, GACGCT, GACGAT, GACGGT, GACGTC, GACGTA, and GACGTG; measuring a signal in response to the contacting; and identifying a species-specific CpG-motif preference when the signal in response to the contacting is consistent with TLR9 signaling. In one embodiment the CpG DNA is an oligodeoxynucleotide having a sequence selected from the group consisting of

(SEQ ID NO:39), TCCATGACGTTTTTGATGTT (SEQ ID NO:40), TCCATAACGTTTTTGATGTT (SEQ ID NO:41), TCCATCACGTTTTTGATGTT (SEQ ID NO:42), TCCATTACGTTTTTGATGTT 25 TCCATGGCGTTTTTGATGTT (SEQ ID NO:43), (SEO ID NO:44), TCCATGCCGTTTTTGATGTT (SEQ ID NO:45), TCCATGTCGTTTTTTGATGTT TCCATGATGTTTTTGATGTT (SEQ ID NO:46), TCCATGAAGTTTTTGATGTT (SEQ ID NO:47), 30 (SEQ ID NO:48), TCCATGAGGTTTTTGATGTT (SEQ ID NO:49), TCCATGACATTTTTGATGTT (SEQ ID NO:50), TCCATGACCTTTTTGATGTT TCCATGACTTTTTTGATGTT (SEQ ID NO:51), TCCATGACGCTTTTGATGTT (SEQ ID NO:52), 35 TCCATGACGATTTTGATGTT (SEQ ID NO:53), TCCATGACGGTTTTGATGTT (SEO ID NO:54),

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TCCATGACGTCTTTGATGTT (SEQ ID NO:55),
TCCATGACGTATTTGATGTT (SEQ ID NO:56), and
TCCATGACGTGTTTGATGTT (SEQ ID NO:57).

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In certain embodiments of the screening methods of the invention, the signal includes expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway. In one embodiment the reporter gene is operatively linked to a promoter sensitive to NF-kB. In one embodiment the signal in response to contacting is binding of the candidate TLR9 ligand or CpG DNA to the polypeptide of the invention.

In one embodiment the screening method is performed on a plurality of test compounds. In one embodiment the response mediated by the TLR9 signal transduction pathway is measured quantitatively and the response mediated by the TLR9 signal transduction pathway associated with each of the plurality of test compounds is compared with a response arising as a result of an interaction between the functional TLR9 and a reference immunostimulatory compound.

Brief Description of the Figures

Figure 1 depicts a Clustal W multiple sequence alignment of deduced amino acid sequences for cat (feline), dog (canine), cow (bovine), mouse (murine), sheep (ovine), pig (porcine), horse (equine), human, and rat TLR9 polypeptides. The deduced amino acid sequences for feline, canine, bovine, murine, ovine, porcine, equine, human, and rat TLR9 polypeptides shown in the figure correspond to SEQ ID NOs 25, 21, 9, 29, 17, 5, 13, 33, and 1, respectively. Lines labeled "multiple" refer to the multiple sequence alignment of all six sequences shown. Lines labeled "mo/hu" refer to a paired sequence alignment of mouse and human TLR9 sequences alone.

Figure 2 is a cladogram depicting an evolutionary relatedness tree for rat, murine, porcine, bovine, equine, and human TLR9 polypeptides in Figure 1.

Figure 3 is a graph depicting species specificity of TLR9 signaling with selected oligonucleotides having strong specificity for human (2006), mouse (5890), or neither (1982).

Detailed Description of the Invention

The present invention provides novel amino acid and nucleotide sequences for TLR9 derived from rat, pig, cow, horse, and sheep. These sequences can be used to identify key features of the primary sequences of these and related TLR molecules, including previously

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known primary sequences of human and mouse (murine) TLR9. Such key features include binding site information and species specificity toward particular CpG motifs. Native and novel chimeric TLR9 polypeptides designed with the aid of this information can be expressed in vitro or in vivo and used in screening assays to identify and to design novel TLR9 ligands. Additionally, the native and novel chimeric TLR9 polypeptides designed with the aid of this information can be expressed in vitro or in vivo and used in screening assays to compare various TLR9 ligands, including CpG DNA.

In one aspect the invention provides isolated TLR9 polypeptides, and isolated nucleic acid molecules encoding them, from rat, pig, cow, horse, and sheep. The term "isolated" as used herein with reference to a nucleic acid molecule or polypeptide means substantially free of or separated from components with which it is normally associated in nature, e.g., other nucleic acids, proteins, lipids, carbohydrates or *in vivo* systems to an extent practical and appropriate for its intended use. In particular, the nucleic acids or polypeptides are sufficiently pure and are sufficiently free from other biological constituents of host cells so as to be useful in, for example, producing pharmaceutical preparations. Because an isolated nucleic acid or polypeptide of the invention may be admixed with a pharmaceutically acceptable carrier in a pharmaceutical preparation, the nucleic acid or polypeptide may represent only a small percentage by weight of such a preparation. The nucleic acid or polypeptide is nonetheless substantially pure in that it has been substantially separated from the substances with which it may be associated in living systems.

An amino acid sequence of rat TLR9 is provided as SEQ ID NO:1. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:1 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of rat TLR9 (See Figure 1). Amino acids numbered 1-821 of SEQ ID NO:1 are presumptively extracellular domain and correspond to SEQ ID NO:2. SEQ ID NO:3 is a nucleotide sequence of rat TLR9 cDNA having an open reading frame corresponding to nucleotides 1-3096. SEQ ID NO:4 is a nucleotide sequence of rat cDNA encoding amino acids 1-821 of SEO ID NO:1.

An amino acid sequence of porcine TLR9 is provided as SEQ ID NO:5. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:5 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of porcine TLR9

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(See Figure 1). Amino acids numbered 1-819 of SEQ ID NO:5 are presumptively extracellular domain and correspond to SEQ ID NO:6. SEQ ID NO:7 is a nucleotide sequence of porcine TLR9 cDNA having an open reading frame corresponding to nucleotides 77-3166. SEQ ID NO:8 is a nucleotide sequence of porcine cDNA encoding amino acids 1-819 of SEQ ID NO:5.

An amino acid sequence of bovine TLR9 is provided as SEQ ID NO:9. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:9 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of bovine TLR9 (See Figure 1). Amino acids numbered 1-818 of SEQ ID NO:9 are presumptively extracellular domain and correspond to SEQ ID NO:10. SEQ ID NO:11 is a nucleotide sequence of bovine TLR9 cDNA having an open reading frame corresponding to nucleotides 84-3170. SEQ ID NO:12 is a nucleotide sequence of bovine cDNA encoding amino acids 1-818 of SEQ ID NO:9.

An amino acid sequence of equine TLR9 is provided as SEQ ID NO:13. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:13 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of equine TLR9 (See Figure 1). Amino acids numbered 1-820 of SEQ ID NO:13 are presumptively extracellular domain and correspond to SEQ ID NO:14. SEQ ID NO:15 is a nucleotide sequence of equine TLR9 cDNA having an open reading frame corresponding to nucleotides 115-3207. SEQ ID NO:16 is a nucleotide sequence of equine cDNA encoding amino acids 1-820 of SEQ ID NO:13.

An amino acid sequence of ovine TLR9 is provided as SEQ ID NO:17. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:17 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of ovine TLR9 (See Figure 1). Amino acids numbered 1-818 of SEQ ID NO:17 are presumptively extracellular domain and correspond to SEQ ID NO:18. SEQ ID NO:19 is a nucleotide sequence of ovine TLR9 cDNA having an open reading frame corresponding to nucleotides 92-3178. SEQ ID NO:20 is a nucleotide sequence of ovine cDNA encoding amino acids 1-818 of SEQ ID NO:17.

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SEQ ID NO:1 (Rat TLR9)

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MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAEPRSNITSLSLIANRI
HHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFLAMRMLEELNLSYNGITTVPRLPSSLTNLSL
SHTNILVLDASSLAGLHSLRVLFMDGNCYYKNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYL
LLSYNLIVKLGAEDLANLTSLRMLDVGGNCRRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN
SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSFKSLVSLQELNMNGIF
FRLLNKNTLRWLAGLPKLHTLHLQMNFINQAQLSVFSTFRALRFVDLSNNRISGPPTLSRVAPEKADEAEKGVPW
PASLTPALPSTPVSKNFMVRCKNLRFTMDLSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLK
VLDLSYNKLDLYHSKSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYSTS
VEYLDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKLSFRDNHLSFFNWSSLA
FLPNLRDLDLAGNLLKALTNGTLPNGTLLQKLDVSSNSIVFVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV
MNLTVLDVSSNPLHCACGAPFVDLLLEVQTKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFGLSLL
AVAVGTVLPLLQHLCGWDVWYCFHLCLAWLPLLTRGRRSAQALPYDAFVVFDKAQSAVADWVYNELRVRLEERRG
RRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDKVSGLLRTSFLLAQQRLLEDRKDVVVLVILRPDA
HRSRYVRLRORLCROSVLFWPHQPNGQGSFWAQLSTALTRDNHHFYNRNFCRGPTAE

SEQ ID NO:2 (Rat TLR9)

MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAEPRSNITSLSLIANRI
HHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFLAMRMLEELNLSYNGITTVPRLPSSLTNLSL
SHTNILVLDASSLAGLHSLRVLFMDGNCYYKNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYL
LLSYNLIVKLGAEDLANLTSLRMLDVGGNCRRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN
SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSFKSLVSLQELNMNGIF
FRLINKNTLRWLAGLPKLHTLHLQMNFINQAQLSVFSTFRALRFVDLSNNRISGPPTLSRVAPEKADEAEKGVPW
PASLTPALPSTPVSKNFMVRCKNLRFTMDLSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLK
VLDLSYNKLDLYHSKSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYSTS
VEYLDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKLSFRDNHLSFFNWSSLA
FLPNLRDLDLAGNLLKALTNGTLPNGTLLQKLDVSSNSIVFVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV
MNLTVLDVSSNPLHCACGAPFVDLLLEVQTKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFG

SEQ ID NO:3 (Rat TLR9)

atgqttctctqtcqcaqqaccctqcaccccttgtctctcctggtacaggccgcagtgctgggctgaggctctggcc ctgggtaccctgccttcctaccctgtgaactgaagcctcatggcctggtagactgcaactggctcttcctg aaqtetgtgcctcacttctctgccgcagaaccccgttccaacatcaccagcctttccttgatcgccaaccgcatc caccacctqcacaacctcgactttgtccacctgcccaacgtgcgacagctgaacctcaagtggaactgtccgccc cctggcctcagcccttgcacttctcctgccgcatgaccattgagcccaaaaccttcctggctatgcgcatgctg gaagagctgaacctgagctataacggtatcaccactgtgccccgcctgcccagctccctgacgaatctgagccta agccaccaccaccatcctggtactcgatgccagcatcctcgctggcctgcacagcctgcgagttctcttcatggac gggaactgctactacaagaacccctgcaacggggcggtgaacgtgaccccggacgccttcctgggcttgagcaac ctcacccacttgtcccttaagtataacaacctcacagaggtgccccgccaactgcccccagcctggagtacctc ctgctgtcctataacctcatcgtcaagctgggggccgaagacctagccaacctgacctcccttcgaatgcttgat gtgggtgggaattgccgtcgctgtgatcacgcccccgacctctgtacagaatgccggcagaagtcccttgatctg caccctcagactttccatcacctgagccaccttgaaggcctggtgctgaaggacagttctctccactcgctgaac tccaagtggttccagggtctggcgaacctctcggtgctggacctaagcgagaactttctctacgagagcatcaac aaaaccaqcqcctttcaqaacctqacccqtctgcgcaagctcgacctgtccttcaattactgcaagaaggtatcg ttcqcccqcctccacctqqcaaqttccttcaagagcctgqtgtcgctgcaggagctgaacatgaacggcatcttc aatttcatcaaccaggcgcagctcagcgtctttagtaccttccgagcccttcgctttgtggacctgtccaataat cqcatcaqcqqqcctccaacqctqtccagaqtcgccccqaaaaggcagacgaggcggagaagggggttccatgg cctgcaagtctcaccccagctctcccgagcactcccgtctcaaagaacttcatggtcaggtgtaagaacctcaga ttcaccatgqacctqtctcqqaacaaccaggtgactatcaagccagagatgttcgtcaacctctcccatctccag tqtctqaqcctgaqccacaactgcatcgcgcaggctgtcaatggctctcagttcctgccgctgaccaacctgaag gtgctggacctgtcctataacaagctggacctgtaccattcgaaatcgttcagtgagctcccacagttgcaggcc

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SEQ ID NO:4 (Rat TLR9)

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ctgggtaccctgccttcctaccctgtgaactgaagcctcatggcctggtagactgcaactggctcttcctg 25 aagtetgtgeeteaettetetgeegeagaacceegtteeaacateaecageettteettgategeeaacegeate caccacctgcacaacctcgactttgtccacctgcccaacgtgcgacagctgaacctcaagtggaactgtccgcc cctggcctcagccccttgcacttctcctgccgcatgaccattgagcccaaaaccttcctggctatgcgcatgctq gaagagctgaacctgagctataacggtatcaccactgtgccccgcctgcccagctccctgacgaatctgagccta agccaccaccaacatcctggtactcgatgccagcagcctcgctggcctgcacagcctgcgagttctcttcatggac 30 gggaactgctactacaagaacccctgcaacggggggtgaacgtgaccccggacgccttcctgggcttgagcaac ctcacccacttgtcccttaaqtataacaacctcacaqaqqtqccccqccaactqcccccaqcctqqaqtacctc ctgctgtcctataacctcatcgtcaagctgggggccgaagacctagccaacctgacctcccttcgaatgcttgat gtgggtgggaattgccgtcgctgtgatcacgccccgacctctgtacagaatgccggcagaagtcccttgatctg caccctcagactttccatcacctgagccaccttgaaggcctggtgctgaaggacagttctctccactcgctgaac 35 tccaagtggttccagggtctggcgaacctctcggtgctggacctaagcgagaactttctctacgagagcatcaac aaaaccagcgcctttcagaacctgacccgtctgcgcaagctcgacctgtccttcaattactgcaagaagqtatcq ttegeeggeteeacetggeaagtteetteaagageetggtgtegetgeaggagetgaacatgaacqqcatette ttccgcttactcaacaagaacacgctcaggtggctggctqgtctqcccaaqctccacacqctqcaccttcaaatq $\verb|aatttcatcaaccaggcgcagctcagcgtctttagtaccttccgagcccttcgctttgtggacctgtccaataat| \\$ 40 cgcatcagcgggcctccaacgctgtccagagtcgcccccgaaaaqqcaqacgaqqcgqaqaaqqqqttccatqq cetgcaagtetcaccccagetetcccgagcactcccgtetcaaagaacttcatggtcaggtgtaagaacctcaga ttcaccatggacctgtctcggaacaaccaggtgactatcaagccagagatgttcgtcaacctctcccatctccaq tgtctgagcctgagccacactgcatcgcgcaggctgtcaatggctctcagttcctgccgctgaccaacctgaaq gtgctggacctgtcctataacaagctggacctgtaccattcgaaatcgttcagtgagctcccacagttqcaqqcc 45 ctggacctgagctacaacagccagccattcagcatgcaggggataggccacaacttcagttttctggccaatctg $\verb|tccaggttacagaaccttagcctggcacacaatgacattcacagccgcgtgtcctcacgcctctacagcacctca|$ gtggagtatetggaetteageggeaaeggtgtgggeegeatgtgggaegaggaggaeetttaeetetatttette caagacctgagaagcctgattcatctggacctgtctcagaataagctgcacatcctccggccccagaacctcaac 50 ttcctgcccaatctgcgagacctggacctggcaggcaatctactaaaqqccctqaccaacqqcaccctqcctaat ggcacgctcctccagaaactggatgtcagtagcaacagtatcgtctttgtggtcccagccttctttgctctggcg gtagagctaaaagaggtcaacctcagccataacatcctcaagactgtggatcgctcctggtttgggcccattgtg atgaacctgacggttctagacgtgagcagcaaccctctgcattgtgcctgcggtgcaccctttqtaqacttactq ctggaagtgcagaccaaggtgcctggctaacggtgtgaagtgtggcagtccccgccagctgcagqqccgc 55 agcatctttgcgcaagacctgcggctgtgcctggatgacgtcctttctcgggactgcttttggc

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SEQ ID NO:5 (Porcine TLR9)

MGPRCTLHPLSLLVQVTALAAALAQGRLPAFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRANVTSLSLLSNRIH
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LSYNHIVTLTPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKDHPKLHSDTFSHLSRLEGLVLKDSSLYNLDT
RWFRGLDRLQVLDLSENFLYDCITKTTAFQGLARLRSLNLSFNYHKKVSFAHLHLAPSFGHLRSLKELDMHGIFF
RSLSETTLQPLVQLPMLQTLRLQMNFINQAQLSIFGAFPGLLYVDLSDNRISGAARPVAITREVDGRERVWLPSR
NLAPRPLDTLRSEDFMPNCKAFSFTLDLSRNNLVTIQSEMFARLSRLECLRLSHNSISQAVNGSQFVPLTSLRVL
DLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASLC
ALDFSGNDLSRMWAEGDLYLRFFQGLRSLVWLDLSQNHLHTLLPRALDNLPKSLKHLHLRDNNLAFFNWSSLTLL
PKLETLDLAGNQLKALSNGSLPSGTQLRRLDLSGNSIGFVNPGFFALAKQLEELNLSANALKTVEPSWFGSMVGN
LKVLDVSANPLHCACGATFVGFLLEVQAAVPGLPSRVKCGSPGQLQGHSIFAQDLRLCLDETLSWNCFGISLLAM
ALGLVVPMLHHLCGWDLWYCFHLCLAWLPHRGQRRGADALFYDAFVVFDKAQSAVADWVYNELRVQLEERRGRRA
LRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPDAYRS
RYVRLRQRLCRQSVLLWPHQPRGQGSFWAQLGTALTRDNHHFYNRNFCRGPTTAE

SEQ ID NO:6 (Porcine TLR9)

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MGPRCTLHPLSLLVQVTALAAALAQGRLPAFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRANVTSLSLLSNRIH
HLHDSDFVHLSSLRTLNLKWNCPPAGLSPMHFPCHMTIEPNTFLAVPTLEELNLSYNSITTVPALPDSLVSLSLS
RTNILVLDPTHLTGLHALRYLYMDGNCYYKNPCQGALEVVPGALLGLGNLTHLSLKYNNLTEVPRSLPPSLETLL
LSYNHIVTLTPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKDHPKLHSDTFSHLSRLEGLVLKDSSLYNLDT
RWFRGLDRLQVLDLSENFLYDCITKTTAFQGLARLRSLNLSFNYHKKVSFAHLHLAPSFGHLRSLKELDMHGIFF
RSLSETTLQPLVQLPMLQTLRLQMNFINQAQLSIFGAFPGLLYVDLSDNRISGAARPVAITREVDGRERVWLPSR
NLAPRPLDTLRSEDFMPNCKAFSFTLDLSRNNLVTIQSEMFARLSRLECLRLSHNSISQAVNGSQFVPLTSLRVL
DLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASLC
ALDFSGNDLSRMWAEGDLYLRFFQGLRSLVWLDLSQNHLHTLLPRALDNLPKSLKHLHLRDNNLAFFNWSSLTLL
PKLETLDLAGNQLKALSNGSLPSGTQLRRLDLSGNSIGFVNPGFFALAKQLEELNLSANALKTVEPSWFGSMVGN
LKVLDVSANPLHCACGATFVGFLLEVQAAVPGLPSRVKCGSPGQLQGHSIFAQDLRLCLDETLSWNCFG

30 SEQ ID NO:7 (Porcine TLR9)

gggcaggctgcctgccttcctgccctgtgagctccagccccacggcctggtgaactgcaactggctcttcctgaa gtccgtgccccacttctcggcggcagcgccccgggccaacgtcaccagcctctccttactctccaaccqcatcca ccacctgcacqactccqacttcqtccacctqtccaqcctacqaactctcaacctcaaqtgqaactqcccqccqqc tggcctcagccccatgcacttcccctgccacatgaccatcgagcccaacaccttcctggccqtgcccaccctgga caactgctactacaagaacccctgccaqqqqqcgctggaggtggtgccgggtgccctcctcggcctgggcaacct cacacatctctcactcaagtacaacaatctcacggaggtgccccgcagcctgcccccagcctggagaccctgct gttgtcctacaaccacattgtcaccctgacgcctgaggacctggccaatctgactgccctgcgcgtgcttgatgt gggggggaactgccgccgctgtgaccatgcccgcaacccctgcagggagtgcccaaaggaccaccccaagctgca ctctgacaccttcagccacctgagccgcctcgaaggcctggtgttgaaagacagttctctctacaacctggacac gaccacggccttccagggcctggcccgactgcgcagcctcaacctgtccttcaattaccacaagaaggtgtcctt tgcccacctgcacctggcaccctcctttqqqcacctccqqtccctqaaqgaqctqqacatqcatqqcatcttctt ccqctcqctcagtgagaccacqctccaacctctqqtccaactqcctatqctccaqaccctqcqcctqcaqatgaa cttcattaaccaggcccagctcagcatctttqqqqccttccctqqcctqctqtacqtqqacctatcqqacaaccq catcagcggagctgcaaggccagtqqccattactagqqaqqtqqatqqtaqqqaqqqqtctqqctqccttccaq gaacctcgctccacqtccactqqacactctccqctcaqaqqacttcatqccaaactqcaagqccttcaqcttcac cttggacctgtctcggaacaacctggtgacaatccagtcggagatgtttgctcgcctctcacgcctcgagtgcct gcgcctgagccacaacagcatctcccaggcggtcaatggctctcagtttgtgccgctgaccagcctgcgggtgct ggacctgtcccacaacaagctggacctqtatcacqqqcqctcqttcacqqagctqccqcqcctqqaaqcactgga cctcagctacaatagccagccctttaccatgcagggtgtgggccacaacctcagcttcgtggcccagctgcccgc

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SEQ ID NO:9 (Bovine TLR9)

MGPYCAPHPLSLLVQAAALAAALAEGTLPAFLPCELOPHGOVDCNWLFLKSVPHFSAGAPRANVTSLSLISNRIH HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS 5 HTSILVLGPTHFTGLHALRFLYMDGNCYYMNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL LSYNHIVTLAPEDLANLTALRVLDVGGNCRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK DWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSFGSLVSLEKLDMHGIFF RSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFVDLSDNRISGAATPAAALGEVDSRVEVWRLPR GLAPGPLDAVSSKDFMPSCNLNFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLD 10 LSHNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP RLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIPGFFVRATRLIELNLSANALKTVDPSWFGSLAGTL KILDVSANPLHCACGAAFVDFLLERQEAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFGLSLLMVA LGLAVPMLHHLCGWDLWYCFHLCLAHLPRRRRQRGEDTLLYDAVVVFDKVQSAVADWVYNELRVQLEERRGRRAL 15 RLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPAAYRSR YVRLRQRLCRQSVLLWPHQPSGQGSFWANLGIALTRDNRHFYNRNFCRGPTTAE

SEQ ID NO:10 (Bovine TLR9)

MGPYCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGAPRANVTSLSLISNRIH

HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS
HTSILVLGPTHFTGLHALRFLYMDGNCYYMNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL
LSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK
DWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSFGSLVSLEKLDMHGIFF
RSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFVDLSDNRISGAATPAAALGEVDSRVEVWRLPR
GLAPGPLDAVSSKDFMPSCNLNFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLD
LSHNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA
LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP
RLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIPGFFVRATRLIELNLSANALKTVDPSWFGSLAGTL
KILDVSANPLHCACGAAFVDFLLERQEAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFG

SEQ ID NO:11 (Bovine TLR9)

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SEQ ID NO:12 (Bovine TLR9)

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- 15 -

SEQ ID NO:13 (Equine TLR9)

MGPCHGALQPLSLLVQAAMLAVALAQGTLPPFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRDNVTSLSLLSNRI HHLHDSDFAQLSNLQKLNLKWNCPPAGLSPMHFPCHMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLIL 5 SRTNILQLDPTSLTGLHALRFLYMDGNCYYKNPCGRALEVAPGALLGLGNLTHLSLKYNNLTTVPRSLPPSLEYL LLSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCVECPHKFPQLHSDTFSHLSRLEGLVLKDSSLYQLN PRWFRGLGNLTVLDLSENFLYDCITKTKAFQGLAQLRRLNLSFNYHKKVSFAHLTLAPSFGSLLSLQELDMHGIF FRSLSQKTLQPLARLPMLQRLYLQMNFINQAQLGIFKDFPGLRYIDLSDNRISGAVEPVATTGEVDGGKKVWLTS RDLTPGPLDTPSSEDFMPSCKNLSFTLDLSRNNLVTVQPEMFAQLSRLQCLRLSHNSISQAVNGSQFVPLTSLQV 10 LDLSHNKLDLYHGRSFTELPRLEALDLSYNSOPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSTSL WALDFSGNSLSQMWAEGDLYLRFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLLRLRNNYLAFFNWSSLTL LPNLETLDLAGNQLKALSNGSLPSGTQLQRLDVSRNSIIFVVPGFFALATRLRELNLSANALRTEEPSWFGFLAG SLEVLDVSANPLHCACGAAFVDFLLQVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDKSLSWDCFGLSLLV VALGLAMPMLHHLCGWDLWYCFHLGLAWLPRRGWQRGADALSYDAFVVFDKAQSAVADWVYNELRVRLEERRGRR 15 ALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDQVSGLLRASFLLAQQRLLEDRKDVVVLVILSPDARR SRYVRLRQRLCRQSVLFWPHQPSGQRSFWAQLGMALTRDNRHFYNQNFCRGPTMAE

SEQ ID NO:14 (Equine TLR9)

MGPCHGALQPLSLLVQAAMLAVALAQGTLPPFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRDNVTSLSLLSNRI
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SRTNILQLDPTSLTGLHALRFLYMDGNCYYKNPCGRALEVAPGALLGLGNLTHLSLKYNNLTTVPRSLPPSLEYL
LLSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCVECPHKFPQLHSDTFSHLSRLEGLVLKDSSLYQLN
PRWFRGLGNLTVLDLSENFLYDCITKTKAFQGLAQLRRLNLSFNYHKKVSFAHLTLAPSFGSLLSLQELDMHGIF
FRSLSQKTLQPLARLPMLQRLYLQMNFINQAQLGIFKDFPGLRYIDLSDNRISGAVEPVATTGEVDGGKKVWLTS
RDLTPGPLDTPSSEDFMPSCKNLSFTLDLSRNNLVTVQPEMFAQLSRLQCLRLSHNSISQAVNGSQFVPLTSLQV
LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSTSL
WALDFSGNSLSQMWAEGDLYLRFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLLRLRNNYLAFFNWSSLTL
LPNLETLDLAGNQLKALSNGSLPSGTQLQRLDVSRNSIIFVVPGFFALATRLRELNLSANALRTEEPSWFGFLAG
SLEVLDVSANPLHCACGAAFVDFLLQVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDKSLSWDCFG

SEQ ID NO:15 (Equine TLR9)

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ctctgttctctgagctgttgccgcgtgaagggactgcgagcacaaagcatcctcctctgcagctgcccagtg tgccagctggaccctctggatcatctcccactccctgtcatgggcccttgccatggtgccctgcagcccctgtct ctcctqqtqcaqqcqccatqctggccgtggctctggcccaaggcaccctgcctcccttcctgccctgtgagctc caqccccacqqcctqqtqaactqcaactggctgttcctqaagtccgtgcccacttctcagcagcagcaccccgg qacaatqtcaccaqcctttccttqctctccaaccqcatccaccacctccacqactccqactttgcccaactgtcc aacctgcagaaactcaacctcaaatggaactgcccgccagccggcctcagccccatgcacttcccctgccacatg accatcgagcccaacactttcctggctgtacccaccctggaggagctgaacctgagctacaacggcatcacgact gtqcctqccctgcccagctccctcgtgtccctgatcctgagccgcaccaacatcctgcagctagaccccaccagc ctggaggtggccccaggcgccctccttggcctgggcaacctcaccacctgtcactcaagtacaacaacctcaca acggtgccccgcagcctgccccctagcctggagtacctgctgttgtcctacaaccacattgtcaccctggcacct aacccctgcgtggagtgcccacataaattcccccagctgcactccgacaccttcagccacctaagccgcctagaa ggcctcgtgttgaaggatagttctctctaccagctgaaccccagatggttccgtggcctgggcaacctcacagtg ctcgacctgagtgagaacttcctctacgactgcatcaccaaaaccaaggcattccagggcctggcccagctgcga agactcaacttgtccttcaattaccataagaaggtgtccttcgcccacctgacgctggcaccctccttcgggagc gcccgcctgcccatgctccagcgtctgtatctgcagatgaacttcatcaaccaggcccagctcggcatcttcaag gacttccctggtctgcgctacatagacctgtcagacaaccgcatcagtggagctgtggagccggtggccaccaca ggggaggtggatggtgggaagaaggtctggctgacatccagggacctcactccaggcccactggacacccccagc tctgaggacttcatgccaagctgcaagaacctcagcttcaccttggacctgtcacggaacaacctggtaacagtc cagccagagatgtttgcccagctctcgcgcctccagtgcctgcgcctgagccacaacagcatctcgcaggcggtc

- 16 -

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SEQ ID NO:16 (Equine TLR9)

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SEQ ID NO:17 (Ovine TLR9)

5 MGPYCAPHPLSLLVQAAALAAALAQGTLPAFLPCELQPRGKVNCNWLFLKSVPRFSAGAPRANVTSLSLISNRIH HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS RTSILVLGPTHFTGLHALRFLYMDGNCYYKNPCQQAVEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL LSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK DWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTQLRRLNLSFNYHKKVSFAHLQLAPSFGGLVSLEKLDMHGIFF 10 RSLTNTTLRPLTQLPKLQSLSLQLNFINQAELSIFGAFPSLLFVDLSDNRISGAARPVAALGEVDSGVEVWRWPR GLAPGPLAAVSAKDFMPSCNLNFTLDLSRNNLVTIOOEMFTRLSRLOCLRLSHNSISOAVNGSOFVPLTRLRVLD LSYNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSKNHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP QLEALDLAGNQLKALSNGSLPPGTRLQKLDVSSNSIGFVTPGFFVLANRLKELNLSANALKTVDPFWFGRLTETL 15 NILDVSANPLHCACGAAFVDFLLEMQAAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFGFSLLMVA LGLAVPMLHHLCGWDLWYCFHLCLAHLPRRRRQRGEDTLLYDAFVVFDKAQSAVADWVYNELRVQLEERRGRRAL RLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAOORLLEDRKDVVVLVILRPAAYRSR YVRLRQRLCRQSVLLWPHQPSGQGSFWANLGMALTRDNRHFYNRNFCRGPTTAE

20 SEQ ID NO:18 (Ovine TLR9)

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MGPYCAPHPLSLLVQAAALAAALAQGTLPAFLPCELQPRGKVNCNWLFLKSVPRFSAGAPRANVTSLSLISNRIH HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS RTSILVLGPTHFTGLHALRFLYMDGNCYYKNPCQQAVEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL LSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK DWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTQLRRLNLSFNYHKKVSFAHLQLAPSFGGLVSLEKLDMHGIFF RSLTNTTLRPLTQLPKLQSLSLQLNFINQAELSIFGAFPSLLFVDLSDNRISGAARPVAALGEVDSGVEVWRWPR GLAPGPLAAVSAKDFMPSCNLNFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTRLRVLD LSYNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSKNHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP QLEALDLAGNQLKALSNGSLPPGTRLQKLDVSSNSIGFVTPGFFVLANRLKELNLSANALKTVDPFWFGRLTETL NILDVSANPLHCACGAAFVDFLLEMQAAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFG

SEQ ID NO:19 (Ovine TLR9)

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25 SEQ ID NO:20 (Ovine TLR9)

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caggcggccgtgcctgggctgtccaggcgcgtcacgtgtggcagtccgggccagctccagggccgcagcatcttcgcaggacctctgcctggatgagaccctctccttggactgcttttggc

Complete nucleotide and amino acid sequences for canine and feline TLR9 are publicly available. For example, an amino acid sequence for canine TLR9 is available as GenBank accession number BAC65192 and its corresponding nucleotide sequence is available as GenBank accession number AB104899. An amino acid sequence for feline TLR9 is available as GenBank accession number AAN15751 and its corresponding nucleotide sequence is available as GenBank accession number AY137581.

Complete nucleotide and amino acid sequences for canine and feline TLR9 were also determined independently from those available from public databases.

An amino acid sequence of canine TLR9 is provided as SEQ ID NO:21. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:21 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of canine TLR9 (See Figure 1). Amino acids numbered 1-822 of SEQ ID NO:21 are presumptively extracellular domain and correspond to SEQ ID NO:22. SEQ ID NO:23 is a nucleotide sequence of canine TLR9 cDNA having an open reading frame corresponding to nucleotides 91-3186. SEQ ID NO:24 is a nucleotide sequence of canine cDNA encoding amino acids 1-822 of SEQ ID NO:21.

An amino acid sequence of feline TLR9 is provided as SEQ ID NO:25. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:25 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of feline TLR9 (See Figure 1). Amino acids numbered 1-820 of SEQ ID NO:25 are presumptively extracellular domain and correspond to SEQ ID NO:26. SEQ ID NO:27 is a nucleotide sequence of feline TLR9 cDNA having an open reading frame corresponding to nucleotides 87-3179. SEQ ID NO:28 is a nucleotide sequence of feline cDNA encoding amino acids 1-820 of SEQ ID NO:25.

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SEQ ID NO:21 (Canine TLR9)

MGPCRGALHPLSLLVQAAALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAAPRGNVTSLSLYSNRI HHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFLAVPTLEDLNLSYNSITTVPALPSSLVSLSL SRTNILVLDPATLAGLYALRFLFLDGNCYYKNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYL

- 20 -

LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKGFPQLHPNTFGHLSHLEGLVLRDSSLYSLD PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSFGSLLSLQELDIHGIF FRSLSKTTLQSLAHLPMLQRLHLQLNFISQAQLSIFGAFPGLRYVDLSDNRISGAAEPAAATGEVEADCGERVWP QSRDLALGPLGTPGSEAFMPSCRTLNFTLDLSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNL RVLDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA SLRALDFSGNTLSQMWAEGDLYLRFFQGLRSLVQLDLSQNRLHTLLPRNLDNLPKSLRLLRLRDNYLAFFNWSSL ALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVPSFFALAVRLRELNLSANALKTVEPSWFGSL AGALKVLDVTANPLHCACGATFVDFLLEVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDEALSWVCFSLSL LAVALSLAVPMLHQLCGWDLWYCFHLCLAWLPRRGRRRGVDALAYDAFVVFDKAQSSVADWVYNELRVQLEERRG RRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILCPDA HRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNRHFYNONFCRGPTTA

SEQ ID NO:22 (Canine TLR9)

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MGPCRGALHPLSLLVQAAALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAAPRGNVTSLSLYSNRI

HHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFLAVPTLEDLNLSYNSITTVPALPSSLVSLSL
SRTNILVLDPATLAGLYALRFLFLDGNCYYKNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYL
LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKGFPQLHPNTFGHLSHLEGLVLRDSSLYSLD
PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSFGSLLSLQELDIHGIF
FRSLSKTTLQSLAHLPMLQRLHLQLNFISQAQLSIFGAFPGLRYVDLSDNRISGAAEPAAATGEVEADCGERVWP
QSRDLALGPLGTPGSEAFMPSCRTLNFTLDLSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNL
RVLDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA
SLRALDFSGNTLSQMWAEGDLYLRFFQGLRSLVQLDLSQNRLHTLLPRNLDNLPKSLRLLRLRDNYLAFFNWSSL
ALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVPSFFALAVRLRELNLSANALKTVEPSWFGSL
AGALKVLDVTANPLHCACGATFVDFLLEVQAAVPGLPSRVKCGSPGOLOGRSIFAODLRLCLDEALSWVCFS

SEQ ID NO:23 (Canine TLR9)

aggaaggggctgtgagctccaagcatcctttcctgcagctgctgcccagcctqccaqccaqaccctctqqaqaaq cccccgctccctgtcatgggcccctgccgtggcgccctgcacccctgtctctcctggtgcaggctgccgcgcta gccctggccctggcccagggcaccctgcctgccttcctgccctgtgagctccagccccatggcctggtgaactgc aactggctgttcctcaagtccgtgccccgcttctcggcagctgcaccccgcggtaacgtcaccagcctttccttq tactccaaccgcatccaccacctccatgactatgactttgtccacttcgtccacctgcggcgtctcaatctcaaq tggaactgcccgcccgccagcctcagccccatgcactttccctgtcacatgaccattgagcccaacaccttcctg gtgtccctgtccctgagccgcaccaacatcctggtgctggaccctgccaccctggcaggcctttatgccctgcgc ttcctgttcctggatggcaactgctactacaaqaaccctqccaqcaqqccctqcaqqtqccccaqqtqccctc ctgggcctgggcaacctcacacacctgtcactcaaqtacaacatctcaccqtqqtqccqcqqqqcctqccccc agcctggagtacctgctcttgtcctacaaccacatcatcaccctggcacctgaggacctggccaatctgactgcc ctgcgtgtcctcgatgtgggtgggaactgtcgccgctgtgaccatgcccgtaacccctgcagggagtgccccaag ggcttcccccagctgcaccccaacaccttcggccacctgagccacctcgaaqqcctqqtqttqaqqqacaqctct tatgactgcatcaccaaaaccaaagccttctacggcctggcccggctgcgcagactcaacctqtccttcaattat cataagaaggtgtcctttgcccacctgcatctggcatcctccttcgggagcctactgtccctgcaggagctggac atacatggcatettetteegetegeteageaagaceaegeteeagtegetggeeeacetgeeeatgeteeagegt ctgcatctgcagttgaactttatcagccaggcccagctcagcatcttcggcgccttccctggactgcggtacgtg gacttgtcagacaaccgcatcagtggagctgcagagcccgcggctgccacaggggaggtagaggcagactgtggg gagagagtetggeeacagtecegggaeettgetetgggeeeaetgggeaeceeeggeteagaggeetteatgeeg agctgcaggaccctcaacttcaccttggacctgtctcggaacaacctagtgactgttcagccggagatgtttgtc cggctggcgcctccagtgcctgggcctgagccacaacagcatctcgcaggcggtcaatggctcgcagttcgtg cctctgagcaacctgcgggtgctggacctgtcccataacaagctggacctgtaccacgggcgctcgttcacggag agctttgtggcacagctgccagccctgcgctacctcagcctggcgcacaatggcatccacagccqcqtqtcccaq cagctccgcagcgcctcgctccgggccctggacttcagtggcaataccctgagccagatgtgggccgagggagac ctctatctccgcttcttccaaggcctgagaagcctggttcagctggacctgtcccagaatcqcctqcataccctc ctgccacgcaacctggacaacctccccaagagcctgcggctcctgcggctccgtgacaattacctggctttcttc aactggagcagcctggccctcctacccaagctggaagccctggacctggcgggaaaccagctqaaqgccctqaqc

aatggcagettgeecaaeggcaeecageteeagaggetggaeeteageggcaaeageateggettegtggteeee agcttttttgccctggccgtgaggcttcgagagctcaacctcagcgccaacgccctcaagacggtggagccctcc tggtttggttccctggcgggtgccctgaaagtcctagacgtgaccgccaaccccttgcattgcgcttgcggcgca 5 ggccagctccagggccgcagcatcttcgcacaggacctgcgcctctgcctggacgaagcgctctcctgggtctgt ttcagcctctcgctgctggctgtggccctgagcctggctgtgcccatgctgcaccagctctgtggctgggacctc gacgccttcgtggtcttcgacaaggcgcagagctcggtggcggactgggtgtacaatgagctgcgggtacagcta gaggagcgccgtgggcgccggggcgctacgcctgtgtctggaggaacgtgactgggtacccggcaaaaccctcttc 10 gagaacetetgggceteagtttacagcagcegcaagacgetgtttgtgetggceegcaeggacagagteagegge ctcctgcgtgccagcttcctgctggcccaacagcgcctgctggaggaccgcaaggacgtcgtggtgctggtgatc $\verb|ctgtgccccgacgcccaccgctatgtgcggctgcgccagcgcctctgccgccagagtgtcctcctctgg|$ $\verb|ccccaccagcccagctggcccagctgggcacggccctgaccagggacaaccgccacttc|$ tacaaccagaacttctgccggggccccacgacagcctgataggcagacagcccagcaccttcgcgcccctacacc 15 etgeetgtetgtetgggatgeeegaeetgetggetetaeaeegeegetetgteteeeetaeaeeeeageeetggea taaagcgaccgctcaataaatgctgctggtagac

SEQ ID NO:24 (Canine TLR9)

20 cagggcaccctgcctgccttcctgccctgtgagctccagccccatggcctggtgaactgcaactggctgttcctc aagtccgtgccccgcttctcggcagctgcaccccgcggtaacgtcaccagcctttccttgtactccaaccgcatc ${\tt gccagcctcagccccatgcactttccctgtcacatgaccattgagcccaacaccttcctggctgtgcccacccta}$ 25 agccgcaccaacatcctggtgctggaccctgccaccctggcaggcctttatgccctgcgcttcctgttcctggat ggcaactgctactacaagaacccctgccagcaggccctgcaggtggccccaggtgccctcctgggcctgggcaac ctcacacacctgtcactcaagtacaaccacctcaccgtggtgccgcggggcctgcccccagcctggagtacctg ctcttgtcctacaaccatcatcaccctggcacctgaggacctggccaatctgactgccctgcgtgtcctcgat gtgggtgggaactgtcgccgctgtgaccatgcccgtaacccctgcagggagtgccccaagggcttcccccagctg 30 aaaaccaaagccttctacggcctggcccggctgcgcagactcaacctgtccttcaattatcataagaaggtgtcc ttccgctcgctcagcaagaccacgctccagtcgctggcccacctgcccatgctccagcgtctgcatctgcagttg 35 aactttatcagccaggcccagctcagcatcttcggcgccttccctggactgcggtacgtggacttgtcagacaac cgcatcagtggagctgcagagcccgcggctgccacaggggaggtagaggcagactgtggggagagagtctggcca cagtcccgggaccttgctctgggcccactgggcacccccggctcagaggccttcatgccgagctgcaggaccctc aacttcaccttggacctgtctcggaacaacctagtgactgttcagccggagatgtttgtccggctggcgcctc cagtgcctgggcctgagccacaacagcatctcgcaggcggtcaatggctcgcagttcgtgcctctgagcaacctg 40 cgggtgctggacctgtcccataacaagctggacctgtaccacgggcgctcgttcacggagctgccgcggctggag gccttggacctcagctacaacagccagcccttcagcatgcggggcgtgggccacaatctcagctttgtggcacag ctgccagccctgcgctacctcagcctggcgcacaatggcatccacagccgcgtgtcccagcagctccgcagcgcc $\verb|tcgctccgggccctggacttcagtggcaataccctgagccagatgtgggccgagggagacctctatctccgcttc|$ ttccaaggcctgagaagcctggttcagctggacctgtcccagaatcgcctgcataccctcctgccacgcaacctg 45 gacaacctccccaagagcctgcggctcctgcggctccgtgacaattacctggctttcttcaactggagcagcctg gccctcctacccaagctggaagccctggacctggcgggaaaccagctgaaggccctgagcaatggcagcttgccc aacggcacccagctccagaggctggacctcagcggcaacagcatcggcttcgtggtccccagcttttttgccctg gccgtgaggcttcgagagctcaacctcagcgccaacgccctcaagacggtggagccctcctggtttggttccctg gegggtgeeetgaaagteetagaegtgaeegeeaaceeettgeattgegettgeggegeaacettegtggaette 50 ttgctggaggtgcaggctgcggtgcccggcctgcctagccgtgtcaagtgcggcagcccgggccagctccagggc cgcagcatcttcgcacaggacctgcgcctctgcctggacgaagcgctctcctgggtctgtttcagc

SEQ ID NO:25 (Feline TLR9)

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MGPCHGALHPLSLLVQAAALAVALAQGTLPAFLPCELQRHGLVNCDWLFLKSVPHFSAAAPRGNVTSLSLYSNRI HHLHDSDFVHLSSLRRLNLKWNCPPASLSPMHFPCHMTIEPHTFLAVPTLEELNLSYNSITTVPALPSSLVSLSL SRTNILVLDPANLAGLHSLRFLFLDGNCYYKNPCPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYL
LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCMECPKGFPHLHPDTFSHLNHLEGLVLKDSSLYNLN
PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSFGSLLSLQQLDMHGIF
FRSLSETTLRSLVHLPMLQSLHLQMNFINQAQLSIFGAFPGLRYVDLSDNRISGAMELAAATGEVDGGERVRLPS
GDLALGPPGTPSSEGFMPGCKTLNFTLDLSRNNLVTIQPEMFARLSRLQCLLLSRNSISQAVNGSQFMPLTSLQV
LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASL
RALDFSGNALSRMWAEGDLYLHFFRGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLRLLRLRDNYLAFFNWSSLVL
LPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVASSFFALATRLRELNLSANALKTVEPSWFGSLAG
TLKVLDVTGNPLHCACGAAFVDFLLEVQAAVPGLPGHVKCGSPGQLQGRSIFAQDLRLCLDEALSWDCFGLSLLT
VALGLAVPMLHHLCGWDLWYCFHLCLAWLPRRGRRRGADALPYDAFVVFDKAQSAVADWVYNELRVRLEERRGRR
ALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPDAHR
SRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNQHFYNQNFCRGPTTAE

SEQ ID NO:26 (Feline TLR9)

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MGPCHGALHPLSLLVQAAALAVALAQGTLPAFLPCELQRHGLVNCDWLFLKSVPHFSAAAPRGNVTSLSLYSNRI HHLHDSDFVHLSSLRRLNLKWNCPPASLSPMHFPCHMTIEPHTFLAVPTLEELNLSYNSITTVPALPSSLVSLSL SRTNILVLDPANLAGLHSLRFLFLDGNCYYKNPCPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYL LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCMECPKGFPHLHPDTFSHLNHLEGLVLKDSSLYNLN PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSFGSLLSLQQLDMHGIF FRSLSETTLRSLVHLPMLQSLHLQMNFINQAQLSIFGAFPGLRYVDLSDNRISGAMELAAATGEVDGGERVRLPS GDLALGPPGTPSSEGFMPGCKTLNFTLDLSRNNLVTIQPEMFARLSRLQCLLLSRNSISQAVNGSQFMPLTSLQV LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASL RALDFSGNALSRMWAEGDLYLHFFRGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLRLLRLRDNYLAFFNWSSLVL LPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVASSFFALATRLRELNLSANALKTVEPSWFGSLAG
TLKVLDVTGNPLHCACGAAFVDFLLEVOAAVPGLPGHVKCGSPGQLQGRSIFAQDLRLCLDEALSWDCFG

SEQ ID NO:27 (Feline TLR9)

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SEQ ID NO:28 (Feline TLR9)

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Complete nucleotide and amino acid sequences for murine and human TLR9 are publicly available. For example, an amino acid sequence of murine TLR9 is available as

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GenBank accession no. AAK29625, provided as SEQ ID NO:29. Amino acids numbered 1-821 of SEQ ID NO:29 presumptively include the entire extracellular domain and correspond to SEQ ID NO:30. SEQ ID NO:31 corresponds to GenBank accession number AF348140, which is a nucleotide sequence of murine TLR9 cDNA. SEQ ID NO:32 is a nucleotide sequence of murine cDNA encoding amino acids 1-821 of SEQ ID NO:29.

An amino acid sequence of human TLR9 is available as GenBank accession no. AAF78037, provided as SEQ ID NO:33. Amino acids numbered 1-820 of SEQ ID NO:33 presumptively include the entire extracellular domain and correspond to SEQ ID NO:34. SEQ ID NO:35 corresponds to GenBank accession number AF245704, which is a nucleotide sequence of human TLR9 cDNA. SEQ ID NO:36 is a nucleotide sequence of human cDNA encoding amino acids 1-820 of SEQ ID NO:33.

SEQ ID NO:29 (Murine TLR9)

MVLRRRTLHPLSLLVQAAVLAETLALGTLPAFLPCELKPHGLVDCNWLFLKSVPRFSAAASCSNITRLSLISNRI 15 HHLHNSDFVHLSNLRQLNLKWNCPPTGLSPLHFSCHMTIEPRTFLAMRTLEELNLSYNGITTVPRLPSSLVNLSL ${\tt SHTNILVLDANSLAGLYSLRVLFMDGNCYYKNPCTGAVKVTPGALLGLSNLTHLSLKYNNLTKVPRQLPPSLEYL}$ LVSYNLIVKLGPEDLANLTSLRVLDVGGNCRRCDHAPNPCIECGQKSLHLHPETFHHLSHLEGLVLKDSSLHTLN SSWFQGLVNLSVLDLSENFLYESINHTNAFQNLTRLRKLNLSFNYRKKVSFARLHLASSFKNLVSLQELNMNGIF FRSLNKYTLRWLADLPKLHTLHLQMNFINQAQLSIFGTFRALRFVDLSDNRISGPSTLSEATPEEADDAEQEELL 20 SADPHPAPLSTPASKNFMDRCKNFKFTMDLSRNNLVTIKPEMFVNLSRLQCLSLSHNSIAQAVNGSQFLPLTNLQ VLDLSHNKLDLYHWKSFSELPQLQALDLSYNSQPFSMKGIGHNFSFVAHLSMLHSLSLAHNDIHTRVSSHLNSNS VRFLDFSGNGMGRMWDEGGLYLHFFQGLSGLLKLDLSQNNLHILRPQNLDNLPKSLKLLSLRDNYLSFFNWTSLS FLPNLEVLDLAGNQLKALTNGTLPNGTLLQKLDVSSNSIVSVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV ${\tt MNLTVLDVRSNPLHCACGAAFVDLLLEVQTKVPGLANGVKCGSPGQLQGRSIFAQDLRLCLDEVLSWDCFGLSLL}$ 25 AVAVGMVVPILHHLCGWDVWYCFHLCLAWLPLLARSRRSAQALPYDAFVVFDKAQSAVADWVYNELRVRLEERRG ${\tt RRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDRVSGLLRTSFLLAQQRLLEDRKDVVVLVILRPDA}$ HRSRYVRLRQRLCRQSVLFWPQQPNGQGGFWAQLSTALTRDNRHFYNONFCRGPTAE

SEQ ID NO:30 (Murine TLR9)

30 MVLRRRTLHPLSLLVQAAVLAETLALGTLPAFLPCELKPHGLVDCNWLFLKSVPRFSAAASCSNITRLSLISNRI HHLHNSDFVHLSNLRQLNLKWNCPPTGLSPLHFSCHMTIEPRTFLAMRTLEELNLSYNGITTVPRLPSSLVNLSL SHTNILVLDANSLAGLYSLRVLFMDGNCYYKNPCTGAVKVTPGALLGLSNLTHLSLKYNNLTKVPRQLPPSLEYL LVSYNLIVKLGPEDLANLTSLRVLDVGGNCRRCDHAPNPCIECGQKSLHLHPETFHHLSHLEGLVLKDSSLHTLN SSWFQGLVNLSVLDLSENFLYESINHTNAFQNLTRLRKLNLSFNYRKKVSFARLHLASSFKNLVSLQELNMNGIF FRSLNKYTLRWLADLPKLHTLHLQMNFINQAQLSIFGTFRALRFVDLSDNRISGPSTLSEATPEEADDAEQEELL SADPHPAPLSTPASKNFMDRCKNFKFTMDLSRNNLVTIKPEMFVNLSRLQCLSLSHNSIAQAVNGSQFLPLTNLQ VLDLSHNKLDLYHWKSFSELPQLQALDLSYNSQPFSMKGIGHNFSFVAHLSMLHSLSLAHNDIHTRVSSHLNSNS VRFLDFSGNGMGRMWDEGGLYLHFFQGLSGLLKLDLSQNNLHILRPQNLDNLPKSLKLLSLRDNYLSFFNWTSLS FLPNLEVLDLAGNQLKALTNGTLPNGTLLQKLDVSSNSIVSVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV MNLTVLDVRSNPLHCACGAAFVDLLLEVQTKVPGLANGVKCGSPGQLQGRSIFAQDLRLCLDEVLSWDCFG

SEQ ID NO:31 (Murine TLR9)

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SEQ ID NO:31 (Murine TLR9)

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SEQ ID NO:33 (Human TLR9)

MGFCRSALHPLSLLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCNWLFLKSVPHFSMAAPRGNVTSLSLSSNRI HHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFLAVPTLEELNLSYNNIMTVPALPKSLISLSL SHTNILMLDSASLAGLHALRFLFMDGNCYYKNPCRQALEVAPGALLGLGNLTHLSLKYNNLTVVPRNLPSSLEYL 25 LLSYNRIVKLAPEDLANLTALRVLDVGGNCRRCDHAPNPCMECPRHFPQLHPDTFSHLSRLEGLVLKDSSLSWLN ASWFRGLGNLRVLDLSENFLYKCITKTKAFQGLTQLRKLNLSFNYQKRVSFAHLSLAPSFGSLVALKELDMHGIF FRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYVDLSDNRISGASELTATMGEADGGEKVWLQP GDLAPAPVDTPSSEDFRPNCSTLNFTLDLSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQV LDLSRNKLDLYHEHSFTELPRLEALDLSYNSQPFGMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQOLCSTSL 30 RALDFSGNALGHMWAEGDLYLHFFQGLSGLIWLDLSQNRLHTLLPQTLRNLPKSLQVLRLRDNYLAFFKWWSLHF LPKLEVLDLAGNRLKALTNGSLPAGTRLRRLDVSCNSISFVAPGFFSKAKELRELNLSANALKTVDHSWFGPLAS ALQILDVSANPLHCACGAAFMDFLLEVQAAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFALSLLA VALGLGVPMLHHLCGWDLWYCFHLCLAWLPWRGRQSGRDEDALPYDAFVVFDKTQSAVADWVYNELRGOLEECRG RWALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAOORLLEDRKDVVVLVILSPDG 35 RRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNHHFYNRNFCOGPTAE

SEQ ID NO:34 (Human TLR9)

MGFCRSALHPLSLLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCNWLFLKSVPHFSMAAPRGNVTSLSLSSNRI HHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFLAVPTLEELNLSYNNIMTVPALPKSLISLS SHTNILMLDSASLAGLHALRFLFMDGNCYYKNPCRQALEVAPGALLGLGNLTHLSLKYNNLTVVPRNLPSSLEYL LLSYNRIVKLAPEDLANLTALRVLDVGGNCRRCDHAPNPCMECPRHFPQLHPDTFSHLSRLEGLVLKDSSLSWLN ASWFRGLGNLRVLDLSENFLYKCITKTKAFQGLTQLRKLNLSFNYQKRVSFAHLSLAPSFGSLVALKELDMHGIF FRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYVDLSDNRISGASELTATMGEADGGEKVWLQP GDLAPAPVDTPSSEDFRPNCSTLNFTLDLSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQV LDLSRNKLDLYHEHSFTELPRLEALDLSYNSQPFGMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCSTSL RALDFSGNALGHMWAEGDLYLHFFQGLSGLIWLDLSQNRLHTLLPQTLRNLPKSLQVLRLRDNYLAFFKWWSLHF LPKLEVLDLAGNRLKALTNGSLPAGTRLRRLDVSCNSISFVAPGFFSKAKELRELNLSANALKTVDHSWFGPLAS ALQILDVSANPLHCACGAAFMDFLLEVQAAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFA

50 SEQ ID NO:35 (Human TLR9)

aggctggtataaaaatcttacttcctctattctctgagccgctgctgcccctgtgggaagggacctcgagtgtgaagcatccttccctgtagctgtcagtctgcccgccagaccctctggagaagcccctgcccccagcatgggtttctgccgcagccgcagcgccatgaccctggccctgggt

accttgcctgccttcctaccctgtgagctccagcccacggcctggtgaactgcaactggctgttcctgaagtct gtgccccacttctccatggcagcaccccgtggcaatgtcaccagcctttccttgtcctccaaccgcatccaccac ctccatgattctgactttgcccacctgcccagcctgcggcatctcaacctcaagtggaactgcccgccggttggc ctcagccccatgcacttcccctgccacatgaccatcgagcccagcaccttcttggctgtgcccaccctggaagag 5 ctaaacctgagctacaacaacatcatgactgtgcctgcgctgcccaaatccctcatatccctgtccctcagccat accaacatcctgatgctagactctgccagcctcgccggcctgcatgccctgcgcttcctattcatggacggcaac tgttattacaagaacccctgcaggcaggcactggaggtggccccggggtgccctccttggcctgggcaacctcacc cacctgtcactcaagtacaacaacctcactgtggtgccccgcaacctgccttccagcctggagtatctgctgttg tcctacaaccgcatcgtcaaactggcgcctgaggacctggccaatctgaccgccctgcgtgtgctcgatgtgggc 10 ggaaattgccgccgctgcgaccacgctcccaacccctgcatggagtgccctcgtcacttcccccagctacatccc gatacetteagecacetgagecgtettgaaggeetggtgttgaaggaeagtteteteteetggetgaatgeeagt aaggccttccagggcctaacacagctgcgcaagcttaacctgtccttcaattaccaaaagagggtgtcctttgcc cacctgtctctggccccttccttcgggagcctggtcgccctgaaggagctggacatgcacggcatcttcttccgc 15 tcactcgatgagaccacgctccggccactggcccgcctgcccatgctccagactctgcgtctgcagatgaacttc atcaaccaggcccagctcggcatcttcagggccttccctggcctgcgctacgtggacctgtcggacaaccgcatc agcggagcttcggagctgacagccaccatgggggaggcagatggaggggagaaggtctggctgcagcctggggac cttgctccggccccagtggacactcccagctctgaagacttcaggcccaactgcagcaccctcaacttcaccttg gatctgtcacggaacaacctggtgaccgtgcagccggagatgtttgcccagctctcgcacctgcagtgcctgcgc $\verb|ctgagccacaactgcatctcgcaggcagtcaatggctcccagttcctgccgctgaccggtctgcaggtgctagac| \\$ 20 ctgtcccgcaataagctggacctctaccacgagcactcattcacggagctaccgcgactggaggccctggacctc agctacaacagccagccctttggcatgcagggcgtgggccacaacttcagcttcgtggctcacctgcgcaccctg cgccacctcagcctggcccacaacaacatccacagccaagtgtcccagcagctctgcagtacgtcgctgcgggcc ctggacttcagcggcaatgcactgggccatatgtgggccgagggagacctctatctgcacttcttccaaggcctg 25 agcggtttgatctggctggacttgtcccagaaccgcctgcacaccctcctgccccaaaccctgcgcaacctcccc aagagcctacaggtgctgcgtctccgtgacaattacctggccttctttaagtggtggagcctccacttcctgccc ctccggaggctggatgtcagctgcaacagcatcagcttcgtggcccccggcttcttttccaaggccaaggagctg cqaqaqctcaaccttagcgccaacgcctcaagacagtggaccactcctggtttgggcccctggcgagtgccctg 30 caaatactagatgtaagcgccaaccctctgcactgcgcctgtggggcggcctttatggacttcctgctggaggtg caggctgccgtgcccggtctgcccagccgggtgaagtgtggcagtccgggccagctccagggcctcagcatcttt ctgggcctgggtgtgcccatgctgcatcacctctgtggctgggacctctggtactgcttccacctgtgcctggcc tggcttccctggcgggggggcaaagtgggcgagatgaggatgccctgccctacgatgccttcgtggtcttcgac aaaacgcagagcgcagtggcagactgggtgtacaacgagcttcgggggcagctggaggagtgccgtgggcgctgg 35 gcactccgcctgtgcctggaggaacgcgactggctgcctggcaaaaccctctttgagaacctgtgggcctcggtc tatggcagccgcaagacgctgtttgtgctggcccacacggaccgggtcagtggtctcttgcgcgccagcttcctg ctggcccagcagcgcctgctggaggaccgcaaggacgtcgtggtgctggtgatcctgagccctgacggccgccgc tecegetaegtgeggetgegeeagegeetetgeegeeagagtgteeteetetggeeeeacageeeagtggteag 40 cgcagcttctgggcccagctgggcatggccctgaccagggacaaccaccacttctataaccggaacttctgccag tggtctgaccctccctgctcgcctccctcaccccacacctgacacagagca

SEQ ID NO:36 (Human TLR9)

45 atgggtttctgccgcagcgccctgcacccgctgtctctcctggtgcaggccatcatgctggccatgaccctggcc ctgggtaccttgcctgccttcctaccctgtgagctccagccccacggcctggtgaactgcaactggctgttcctg aagtetgtgeeceaetteteeatggeageaceegtggeaatgteaceageettteettgteeteeaacegeate caccacctccatgattctgactttgcccacctgcccagcctgcggcatctcaacctcaagtggaactgcccgccg gttggcctcagccccatgcacttcccctgccacatgaccatcgagcccagcaccttcttggctgtgcccaccctg 50 gaagagetaaacetgagetacaacaacatcatgactgtgcctgcgctgcccaaatccctcatatccctgtccctc agccataccaacatcctgatgctagactctgccagcctcgccggcctgcatgccctgcgcttcctattcatggac ggcaactgttattacaagaacccctgcaggcaggcactggaggtggccccggggtgccctccttggcctgggcaac ctcacccacctgtcactcaagtacaaccacctcactgtggtgccccgcaacctgccttccagcctggagtatctg ctgttgtcctacaaccgcatcgtcaaactggcgcctgaggacctggccaatctgaccgccctgcgtgtgctcgat 55 gtgggeggaaattgeegeegetgegaeeaegeteeeaaeeeetgeatggagtgeeetegteaetteeeeeageta

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aaaaccaaggccttccagggcctaacacagctgcgcaagcttaacctgtccttcaattaccaaaaqaggqtqtcc $\verb|tttgcccacctgtctctggcccttccttcgggagcctggtcgccctgaaggagctggacatgcacggcatcttc| \\$ ttccgctcactcgatgagaccacgctccggccactggcccgcctgcccatgctccagactctgcgtctgcagatg aacttcatcaaccaggcccagctcggcatcttcagggccttccctggcctgcgctacgtggacctgtcggacaac cgcatcagcggagcttcggagctgacagccaccatgggggaggcagatggaggggagaaggtctggctgcagcct ggggaccttgctccggccccagtggacactcccagctctgaagacttcaggcccaactgcagcaccctcaacttc accttggatctgtcacggaacaacctggtgaccgtgcagccggagatgtttgcccagctctcqcacctqcaqtqc ctgcgcctgagccacaactgcatctcgcaggcagtcaatggctcccagttcctgccgctgaccggtctgcaggtq ctagacctgtcccgcaataagctggacctctaccacgagcactcattcacggagctaccgcgactgqaqqccctq gacctcagctacaacagccagccctttggcatgcagggcgtgggccacaacttcagcttcgtggctcacctqcqc accetgegecaceteageetggeecacaacaacatecacagecaagtgteecageagetetgeagtacgtegetg cgggccctggacttcagcggcaatgcactgggccatatgtgggccgagggagacctctatctgcacttcttccaa ggcctgagcggtttgatctggctggacttgtcccagaaccgcctgcacaccctcctgccccaaaccctgcgcaac ctccccaagagcctacaggtgctgcgtctccgtgacaattacctggccttctttaagtggtggagcctccacttc accoggetccggaggctggatgtcagctgcaacagcatcagcttcgtggcccccggcttcttttccaaggccaag gagctgcgagagctcaaccttagcgccaacgccctcaagacagtggaccactcctggtttgggcccctggcgagt gccctgcaaatactagatgtaagcgccaaccctctgcactgcgcctgtggggcggcctttatggacttcctgctg gaggtgcaggctgccgtgcccggtctgcccagccgggtgaagtgtggcagtccgggccagctccagggcctcaqc atctttgcacaggacctgcgcctctgcctggatgaggccctctcctgggactgtttcgcc

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In addition to the foregoing native rat, porcine, bovine, equine, and ovine TLR9 polypeptides and nucleic acid molecules encoding them, chimeric TLR9 polypeptides and nucleic acid molecules encoding them are provided by the invention. The chimeric polypeptides include at least one amino acid substitution based on a comparison of conserved and non-conserved amino acids among at least two of rat, murine, porcine, bovine, equine, ovine, canine, feline, and human TLR9. The information contained in a multiple sequence alignment of these various TLR9 polypeptide sequences, provided for example in Figure 1, can be used to identify and select individual amino acid positions and even individual amino acids to substitute in designing a chimeric TLR9. The substitution or substitutions can be effected using methods known to those of ordinary skill in molecular biology. Nucleic acids encoding the native or chimeric polypeptides of the invention can be inserted into an expression vector and used to express TLR9 polypeptide.

A conservative amino acid substitution shall refer to a substitution of a first amino acid for a second amino acid, wherein side chains of the first amino acid and the second amino acid share similar features in terms of hydrophobicity, size, aromaticity, or tendency to alter conformation. For example, conservative amino acid substitutions generally may be made between members within each of the following groups: hydrophobic (A, I, L, M, V), neutral (C, S, T), acidic (D, E), basic (H, K, N, Q, R), and aromatic (F, W, Y). A non-conservative amino acid substitution refers to any other amino acid substitution.

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An expression vector for TLR9 will include at least a nucleotide sequence coding for a TLR9, or a fragment thereof coding for a functional TLR9 polypeptide, operably linked to a gene expression sequence which can direct the expression of the TLR9 nucleic acid within a eukaryotic or prokaryotic cell. A "gene expression sequence" is any regulatory nucleotide sequence, such as a promoter sequence or promoter-enhancer combination, which facilitates the efficient transcription and translation of the nucleic acid to which it is operably linked. With respect to TLR9 nucleic acid, the "gene expression sequence" is any regulatory nucleotide sequence, such as a promoter sequence or promoter-enhancer combination, which facilitates the efficient transcription and translation of the TLR9 nucleic acid to which it is operably linked. The gene expression sequence may, for example, be a mammalian or viral promoter, such as a constitutive or inducible promoter. Constitutive mammalian promoters include, but are not limited to, the promoters for the following genes: hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase, β-actin promoter, and other constitutive promoters. Exemplary viral promoters which function constitutively in eukaryotic cells include, for example, promoters from the simian virus (e.g., SV40), papillomavirus, adenovirus, human immunodeficiency virus (HIV), Rous sarcoma virus (RSV), cytomegalovirus (CMV), the long terminal repeats (LTR) of Moloney murine leukemia virus and other retroviruses, and the thymidine kinase (TK) promoter of herpes simplex virus. Other constitutive promoters are known to those of ordinary skill in the art. The promoters useful as gene expression sequences of the invention also include inducible promoters. Inducible promoters are expressed in the presence of an inducing agent. For example, the metallothionein (MT) promoter is induced to promote transcription and translation in the presence of certain metal ions. Other inducible promoters are known to those of ordinary skill in the art.

In general, the gene expression sequence shall include, as necessary, 5' non-transcribing and 5' non-translating sequences involved with the initiation of transcription and translation, respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Especially, such 5' non-transcribing sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined nucleic acid coding sequence for a TLR9 polypeptide. The gene expression sequences optionally include enhancer sequences or upstream activator sequences as desired.

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Generally a nucleic acid coding sequence and a gene expression sequence are said to be "operably linked" when they are covalently linked in such a way as to place the transcription and/or translation of the nucleic acid coding sequence under the influence or control of the gene expression sequence. Thus the TLR9 nucleic acid coding sequence and the gene expression sequence are said to be "operably linked" when they are covalently linked in such a way as to place the transcription and/or translation of the TLR9 nucleic acid coding sequence under the influence or control of the gene expression sequence. If it is desired that the TLR9 sequence be translated into a functional protein, two DNA sequences are said to be operably linked if induction of a promoter in the 5' gene expression sequence results in the transcription of the TLR9 sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the TLR9 sequence, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a gene expression sequence would be operably linked to a TLR9 nucleic acid sequence if the gene expression sequence were capable of effecting transcription of that TLR9 nucleic acid sequence such that the resulting transcript might be translated into the desired TLR9 protein or polypeptide.

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A "TLR9 ligand" as used herein refers to a molecule that specifically binds a TLR9 polypeptide. In one embodiment the TLR9 ligand specifically binds a TLR9 polypeptide corresponding to at least a ligand-binding portion of the extracellular domain of TLR9. In most instances a TLR9 ligand will also induce TLR9 signaling when contacted with TLR9 under suitable conditions. TLR9 signaling refers to TLR/IL-1R signal transduction mediated through the TLR9, as described in further detail elsewhere herein. As mentioned above, CpG nucleic acids have been reported to be TLR9 ligands, but TLR9 ligands may include other entities as well, including, for example, small molecules. As also previously mentioned, there appears to be a species-specific preference for at least certain TLR9s and certain CpG motifs. As used herein, a species-preferred CpG DNA refers to a particular CpG DNA that is optimized for signal induction by a TLR9 of a particular species. A CpG DNA that is optimized for signal induction by a TLR9 of a particular species refers to a CpG DNA having a sequence that preferentially binds to and/or induces signaling by TLR9 of that species. For example, a human-preferred CpG DNA shall refer to a CpG DNA that optimally stimulates human TLR9 to signal through its TIR domain. Likewise, a murine-preferred CpG DNA

shall refer to a CpG DNA that optimally stimulates murine TLR9 to signal through its TIR domain. Examples of human-preferred and murine-preferred CpG DNA are ODN 2006 (SEQ ID NO:58) and 1668 (SEQ ID NO:60), respectively.

The binding and species specificity of TLR9s are believed to be influenced by key amino acids present in the extracellular domain of TLR9. Key amino acids in a TLR9 as used herein refer to those amino acids which contribute significantly to ligand binding and ligand specificity of a particular TLR9 polypeptide.

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A "CpG nucleic acid" or a "CpG immunostimulatory nucleic acid" as used herein is a nucleic acid containing at least one unmethylated CpG dinucleotide (cytosine-guanine dinucleotide sequence, i.e., "CpG DNA" or DNA containing a 5' cytosine followed by 3' guanine and linked by a phosphate bond) which activates a component of the immune system. The entire CpG nucleic acid can be unmethylated or portions may be unmethylated but at least the C of the 5' CG 3' must be unmethylated.

In one embodiment a CpG nucleic acid is represented by at least the formula:

5'-N₁X₁CGX₂N₂-3'

wherein X_1 and X_2 are nucleotides, N is any nucleotide, and N_1 and N_2 are nucleic acid sequences composed of from about 0-25 N's each. In some embodiments X_1 is adenine, guanine, or thymine and/or X_2 is cytosine, adenine, or thymine. In other embodiments X_1 is cytosine and/or X_2 is guanine.

Nucleic acids having modified backbones, such as phosphorothioate backbones, also fall within the class of immunostimulatory nucleic acids. U.S. Pat. Nos. 5,723,335 and 5,663,153 issued to Hutcherson, et al. and related PCT publication WO95/26204 describe immune stimulation using phosphorothioate oligonucleotide analogues. These patents describe the ability of the phosphorothioate backbone to stimulate an immune response in a non-sequence specific manner.

An immunostimulatory nucleic acid molecule, including for example a CpG DNA, may be double-stranded or single-stranded. Generally, double-stranded molecules may be more stable *in vivo*, while single-stranded molecules may have increased activity. The terms "nucleic acid" and "oligonucleotide" refer to multiple nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., cytosine (C), thymine (T) or uracil (U)) or a substituted purine (e.g., adenine (A) or guanine (G)) or a modified base. As

used herein, the terms "nucleic acid" and "oligonucleotide" refer to oligoribonucleotides as well as oligodeoxyribonucleotides. The terms shall also include polynucleosides (i.e., a polynucleotide minus the phosphate) and any other organic base-containing polymer. The terms "nucleic acid" and "oligonucleotide" also encompass nucleic acids or oligonucleotides with a covalently modified base and/or sugar. For example, they include nucleic acids having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 2' position and other than a phosphate group at the 5' position. Thus modified nucleic acids may include a 2'-O-alkylated ribose group. In addition, modified nucleic acids may include sugars such as arabinose instead of ribose. Thus the nucleic acids may be heterogeneous in backbone composition thereby containing any possible combination of polymer units linked together such as peptide-nucleic acids (which have amino acid backbone with nucleic acid bases). In some embodiments the nucleic acids are homogeneous in backbone composition.

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The substituted purines and pyrimidines of the immunostimulatory nucleic acids include standard purines and pyrimidines such as cytosine as well as base analogs such as C-5 propyne substituted bases. Wagner RW et al. (1996) *Nat Biotechnol* 14:840-4. Purines and pyrimidines include but are not limited to adenine, cytosine, guanine, thymine, 5-methylcytosine, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, and other naturally and non-naturally occurring nucleobases, substituted and unsubstituted aromatic moieties.

The immunostimulatory nucleic acid is a linked polymer of bases or nucleotides. As used herein with respect to linked units of a nucleic acid, "linked" or "linkage" means two entities are bound to one another by any physicochemical means. Any linkage known to those of ordinary skill in the art, covalent or non-covalent, is embraced. Such linkages are well known to those of ordinary skill in the art. Natural linkages, which are those ordinarily found in nature connecting the individual units of a nucleic acid, are most common. The individual units of a nucleic acid may be linked, however, by synthetic or modified linkages.

Whenever a nucleic acid is represented by a sequence of letters it will be understood that the nucleotides are in 5' to 3' (or equivalent) order from left to right and that "A" denotes adenine, "C" denotes cytosine, "G" denotes guanine, "T" denotes thymidine, and "U" denotes uracil unless otherwise noted.

Immunostimulatory nucleic acid molecules useful according to the invention can be obtained from natural nucleic acid sources (e.g., genomic nuclear or mitochondrial DNA or cDNA), or are synthetic (e.g., produced by oligonucleotide synthesis). Nucleic acids isolated from existing nucleic acid sources are referred to herein as native, natural, or isolated nucleic acids. The nucleic acids useful according to the invention may be isolated from any source, including eukaryotic sources, prokaryotic sources, nuclear DNA, mitochondrial DNA, etc. Thus, the term nucleic acid encompasses both synthetic and isolated nucleic acids.

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The immunostimulatory nucleic acids can be produced on a large scale in plasmids, (see *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989) and separated into smaller pieces or administered whole. After being administered to a subject the plasmid can be degraded into oligonucleotides. One skilled in the art can purify viral, bacterial, eukaryotic, etc. nucleic acids using standard techniques, such as those employing restriction enzymes, exonucleases or endonucleases.

For use in the instant invention, the immunostimulatory nucleic acids can be synthesized *de novo* using any of a number of procedures well known in the art. For example, the β-cyanoethyl phosphoramidite method (Beaucage SL and Caruthers MH, *Tetrahedron Let* 22:1859 (1981)); nucleoside H-phosphonate method (Garegg et al., *Tetrahedron Let* 27:4051-4054 (1986); Froehler et al., *Nucl Acid Res* 14:5399-5407 (1986); Garegg et al., *Tetrahedron Let* 27:4055-4058 (1986); Gaffney et al., *Tetrahedron Let* 29:2619-2622 (1988)). These chemistries can be performed by a variety of automated oligonucleotide synthesizers available in the market.

The immunostimulatory nucleic acid may be any size of at least 6 nucleotides but in some embodiments are in the range of between 6 and 100 or in some embodiments between 8 and 35 nucleotides in size. Immunostimulatory nucleic acids can be produced on a large scale in plasmids. These may be administered in plasmid form or alternatively they can be degraded into oligonucleotides before administration.

A "stabilized immunostimulatory nucleic acid" shall mean a nucleic acid molecule that is relatively resistant to *in vivo* degradation (e.g., via an exo- or endo-nuclease). Stabilization can be a function of length or secondary structure. Nucleic acids that are tens to hundreds of kbs long are relatively resistant to *in vivo* degradation. For shorter nucleic acids, secondary structure can stabilize and increase their effect. For example, if the 3' end of an

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oligonucleotide has self-complementarity to an upstream region, so that it can fold back and form a sort of stem loop structure, then the oligonucleotide becomes stabilized and therefore exhibits more activity.

Some stabilized immunostimulatory nucleic acids have a modified backbone. It has been demonstrated that modification of the oligonucleotide backbone provides enhanced activity of the immunostimulatory nucleic acids when administered *in vivo*. Nucleic acids, including at least two phosphorothioate linkages at the 5' end of the oligonucleotide and multiple phosphorothioate linkages at the 3' end, preferably 5, may provide maximal activity and protect the oligonucleotide from degradation by intracellular exo- and endo-nucleases. Other modified oligonucleotides include phosphodiester modified oligonucleotide, combinations of phosphodiester and phosphorothioate oligonucleotide, methylphosphonate, methylphosphorothioate, phosphorodithioate, and combinations thereof. Each of these combinations and their particular effects on immune cells is discussed in more detail in U.S. Pat. Nos. 6,194,388 and 6,207,646, the entire contents of which are incorporated herein by reference. It is believed that these modified oligonucleotides may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization. Both phosphorothioate and phosphodiester nucleic acids are active in immune cells.

Other stabilized immunostimulatory nucleic acids include: nonionic DNA analogs, such as alkyl- and aryl-phosphates (in which the charged phosphonate oxygen is replaced by an alkyl or aryl group), phosphodiester and alkylphosphotriesters, in which the charged oxygen moiety is alkylated. Oligonucleotides which contain diol, such as tetraethyleneglycol or hexaethyleneglycol, at either or both termini have also been shown to be substantially resistant to nuclease degradation.

Phosphorothioate nucleic acid molecules may be synthesized using automated techniques employing either phosphoramidate or H-phosphonate chemistries. Aryl- and alkyl-phosphonates can be made, e.g., as described in U.S. Pat. No. 4,469,863; and alkylphosphotriesters (in which the charged oxygen moiety is alkylated as described in U.S. Pat. No. 5,023,243 and European Patent No. 092,574) can be prepared by automated solid phase synthesis using commercially available reagents. Methods for making other DNA backbone modifications and substitutions have been described. Uhlmann E and Peyman A (1990) Chem Rev 90:544; Goodchild J (1990) Bioconjugate Chem 1:165.

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Other sources of immunostimulatory nucleic acids useful according to the invention include standard viral and bacterial vectors, many of which are commercially available. In its broadest sense, a "vector" is any nucleic acid material which is ordinarily used to deliver and facilitate the transfer of nucleic acids to cells. The vector as used herein may be an empty vector or a vector carrying a gene which can be expressed. In the case when the vector is carrying a gene the vector generally transports the gene to the target cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In this case the vector optionally includes gene expression sequences to enhance expression of the gene in target cells such as immune cells, but it is not required that the gene be expressed in the cell.

Nucleic acid-binding fragments of TLRs are believed to include the extracytoplasmic (extracellular) domain or subportions thereof, such as those which include at least an MBD motif, a CXXC motif, or both an MBD motif and a CXXC motif.

Both mouse and human TLR9 have an N-terminal extension of approximately 180 amino acids compared to other TLRs. An insertion also occurs at amino acids 253-268, which is not found in TLRs 1-6 but is present in human TLR7 and human TLR8. This insert has two CXXC motifs which participate in forming a CXXC domain. The CXXC domain resembles a zinc finger motif and is found in DNA-binding proteins and in certain specific CpG binding proteins, e.g., methyl-CpG binding protein-1 (MBD-1). Fujita N et al. (2000) *Mol Cell Biol* 20:5107-18. Both human and mouse TLR9 CXXC domains occur at aa 253-268:

CXXC motif: GNCXXCXXXXXXCXXC SEQ ID NO:62

Human TLR9: GNCRRCDHAPNPCMEC SEQ ID NO:63

25 Murine TLR9: GNCRRCDHAPNPCMIC SEQ ID NO:64

An additional motif believed to be involved in CpG binding is the MBD motif, also found in MBD-1, listed below as SEQ ID NO:53. Fujita, N et al.(2000) *Mol Cell Biol* 20:5107-18; Ohki I et al. (1999) *EMBO J* 18:6653-61. Amino acids 524-554 of hTLR9 and aa 525-555 of mTLR9 correspond to the MBD motif of MBD-1 as shown:

MBD motif:

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	MBD-1	R-XXXXXXX-R-X-D-X-Y-XXXXXXXXX-R-S-XXXXXXX-Y	SEQ ID NO:65
	hTLR9	Q-XXXXXXX-K-X-D-X-Y-XXXXXXXXXX-R-L-XXXXXXX-Y	SEQ ID NO:66
	mTLR9	Q-XXXXXXX-K-X-D-X-Y-XXXXXXXXXX-Q-L-XXXXXXX-Y	SEQ ID NO:67
5	hTLR9	Q-VLDLSRN-K-L-D-L-Y-HEHSFTELP-R-L-EALDLS-Y	SEQ ID NO:68
	mTLR9	Q-VLDLSHN-K-L-D-L-Y-HWKSFSELP-Q-L-QALDLS-Y	SEQ ID NO:69

Although the signaling functions of MBD-1 and TLR9 are quite different, the core D-X-Y is conserved and is believed to be involved in CpG binding.

According to another aspect of the invention, a screening method is provided for identifying an immunostimulatory compound. The method according to this aspect of the invention involves contacting a functional TLR9 with a test compound; detecting presence or absence of a response mediated by a TLR9 signal transduction pathway in the presence of the test compound arising as a result of an interaction between the functional TLR9 and the test compound; and determining the test compound is an immunostimulatory compound when the presence of a response mediated by the TLR9 signal transduction pathway is detected.

An immunostimulatory compound is a natural or synthetic compound that is capable of inducing an immune response when contacted with an immune cell. A TLR9 ligand that is an immunostimulatory compound is a natural or synthetic compound that is capable of inducing an immune response when contacted with an immune cell that expresses TLR9. A TLR9 ligand that is an immunostimulatory compound is also a natural or synthetic compound that is capable of inducing a TLR/IL-1R signal transduction pathway when contacted with a TLR9. Immunostimulatory compounds include but are not limited to immunostimulatory nucleic acids. The immunostimulatory compound can be, for example, a nucleic acid molecule, polynucleotide or oligonucleotide, a polypeptide or oligopeptide, a lipid or lipopolysaccharide, a small molecule.

A basis for certain of the screening assays is the presence of a functional TLR9 in a cell. The functional TLR9 in some instances is naturally expressed by a cell. In other instances, expression of the functional TLR9 can involve introduction or reconstitution of a species-specific TLR9 into a cell or cell line that otherwise lacks the TLR9 or lacks responsiveness to immunostimulatory nucleic acid, resulting in a cell or cell line capable of activating the TLR/IL-1R signaling pathway in response to contact with an

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immunostimulatory nucleic acid. In yet other instances, expression of the functional TLR9 can involve introduction of a chimeric or modified TLR9 into a cell or cell line that otherwise lacks the TLR9 or lacks responsiveness to immunostimulatory nucleic acid, resulting in a cell or cell line capable of activating the TLR/IL-1R signaling pathway in response to contact with an immunostimulatory nucleic acid. Examples of cell lines lacking TLR9 or immunostimulatory nucleic acid responsiveness include, but are not limited to, 293 fibroblasts (ATCC CRL-1573), MonoMac-6, THP-1, U937, CHO, and any TLR9 knock-out. The introduction of the species-specific, chimeric or modified TLR9 into the cell or cell line is preferably accomplished by transient or stable transfection of the cell or cell line with a TLR9-encoding nucleic acid sequence operatively linked to a gene expression sequence (as described above). Methods for transient and for stable transfection of a cell are well known in the art.

The screening assays can have any of a number of possible readout systems based upon either TLR/IL-1R signaling pathway or other assays useful for assessing response to immunostimulatory nucleic acids. It has been reported that immune cell activation by CpG immunostimulatory sequences is dependent in some way on endosomal processing.

In certain embodiments, the readout for the screening assay is based on the use of native genes or, alternatively, cotransfected or otherwise co-introduced reporter gene constructs which are responsive to the TLR/IL-1R signal transduction pathway involving MyD88, TRAF, p38, and/or ERK. Häcker H et al. (1999) *EMBO J* 18:6973-6982. These pathways activate kinases including κB kinase complex and c-Jun N-terminal kinases. Thus reporter genes and reporter gene constructs particularly useful for the assays can include a reporter gene operatively linked to a promoter sensitive to NF-κB. Examples of such promoters include, without limitation, those for NF-κB, IL-1β, IL-6, IL-8, IL-12 p40, CD80, CD86, and TNF-α. The reporter gene operatively linked to the TLR-sensitive promoter can include, without limitation, an enzyme (e.g., luciferase, alkaline phosphatase, β-galactosidase, chloramphenicol acetyltransferase (CAT), etc.), a bioluminescence marker (e.g., greenfluorescent protein (GFP, U.S. Pat. No. 5,491,084), blue fluorescent protein, etc.), a surface-expressed molecule (e.g., CD25), and a secreted molecule (e.g., IL-8, IL-12 p40, TNF-α). In certain embodiments the reporter is selected from IL-8, TNF-α, NF-κB-luciferase (NF-κB-luc; Häcker H et al. (1999) *EMBO J* 18:6973-6982), IL-12 p40-luc (Murphy TL et al. (1995)

Mol Cell Biol 15:5258-5267), and TNF-luc (Häcker H et al. (1999) EMBO J 18:6973-6982). At least one of these reporter constructs (NF-κB-luc) is commercially available (Stratagene, La Jolla, CA). In assays relying on enzyme activity readout, substrate can be supplied as part of the assay, and detection can involve measurement of chemiluminescence, fluorescence, color development, incorporation of radioactive label, drug resistance, or other marker of enzyme activity. For assays relying on surface expression of a molecule, detection can be accomplished using FACS analysis or functional assays. Secreted molecules can be assayed using enzyme-linked immunosorbent assay (ELISA) or bioassays. Many such readout systems are well known in the art and are commercially available.

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According to one embodiment of this method, comparison can be made to a reference immunostimulatory nucleic acid. The reference immunostimulatory nucleic acid may be any suitably selected immunostimulatory nucleic acid, including a CpG nucleic acid. In certain embodiments the screening method is performed using a plurality of test nucleic acids. In certain embodiments comparison of test and reference responses is based on comparison of quantitative measurements of responses in each instance.

In another aspect the invention provides a screening method for identifying species specificity of an immunostimulatory nucleic acid. The method involves contacting a TLR9 of a first species with a test immunostimulatory nucleic acid; contacting a TLR9 of a second species with the test immunostimulatory nucleic acid; measuring a response mediated by a TLR signal transduction pathway associated with the contacting the TLR9 of the first species with the test immunostimulatory nucleic acid; measuring a response mediated by the TLR signal transduction pathway associated with the contacting the TLR9 of the second species with the test immunostimulatory nucleic acid; and comparing the two responses. The TLR9 may be expressed by a cell or it may be part of a cell-free system. The TLR9 may be part of a complex, with either another TLR or with another protein, e.g., MyD88, IRAK, TRAF, IkB, NF-kB, or functional homologues and derivatives thereof. Thus for example a given ODN can be tested against a panel of human fibroblast 293 fibroblast cells transfected with TLR9 from various species and optionally cotransfected with a reporter construct sensitive to TLR/IL-1R activation pathways. Thus in another aspect, the invention provides a method for screening species selectivity with respect to a given nucleic acid sequence.

Test compounds can include but are not limited to peptide nucleic acids (PNAs), antibodies, polypeptides, carbohydrates, lipids, hormones, and small molecules. Test

compounds can further include variants of a reference immunostimulatory nucleic acid incorporating any one or combination of the substitutions described above. Test compounds can be generated as members of a combinatorial library of compounds.

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In preferred embodiments, the screening methods can be performed on a large scale and with high throughput by incorporating, e.g., an array-based assay system and at least one automated or semi-automated step. For example, the assays can be set up using multiple-well plates in which cells are dispensed in individual wells and reagents are added in a systematic manner using a multiwell delivery device suited to the geometry of the multiwell plate.

Manual and robotic multiwell delivery devices suitable for use in a high throughput screening assay are well known by those skilled in the art. Each well or array element can be mapped in a one-to-one manner to a particular test condition, such as the test compound. Readouts can also be performed in this multiwell array, preferably using a multiwell plate reader device or the like. Examples of such devices are well known in the art and are available through commercial sources. Sample and reagent handling can be automated to further enhance the throughput capacity of the screening assay, such that dozens, hundreds, thousands, or even millions of parallel assays can be performed in a day or in a week. Fully robotic systems are known in the art for applications such as generation and analysis of combinatorial libraries of synthetic compounds. See, for example, U.S. Pat. Nos. 5,443,791 and 5,708,158.

The following examples are provided for illustrative purposes and are not meant to be limiting in any way.

Examples

Example 1. Cloning and Sequencing of Rat, Porcine, Bovine, Equine, Ovine, Canine, and Feline TLR9

Cells and Tissues. Lymphoid tissues, primarily spleen or blood mononuclear cells (PBMC) from five mammalian species were collected: mouse, pig, bovine, rat and horse. Spleen samples were collected in RNAlaterTM (Ambion[®], Austin, TX, USA), stabilized at 4°C overnight and stored at -70°C. Blood samples were centrifuged at 500 x g for 25 min at room temperature and the buffy coat, containing enriched PBMC, was then removed and stored at -70°C. The mouse specimen was used as a comparative positive control.

First-strand cDNA synthesis. Total RNA from the spleen and PBMC samples was isolated using a monophasic solution of phenol and guanidine isothiocyanate: TRIzolTM reagent (GIBCO BRL[®], Burlington, ON, Canada) according to the manufacturer's instructions. First-strand cDNA was synthesized from the total RNA using SUPERSCRIPTTM II reverse transcriptase (GIBCO BRL[®], Burlington, ON, Canada). Approximately 3 μg of total RNA was added to 50 pmoles of oligo(dT) primer [poly T₍₁₈₎]; the mixture was heated to 70°C for 10 min and subsequently chilled on ice. The following was added to the cooled reaction mixture: 1 μl of mixed dNTP stock containing 10 mM each dATP, dCTP, dGTP and dTTP (Amersham Pharmacia Biotech Inc., Baie de Urfe, Quebec) at neutral pH, 1X first strand buffer (50 mM Tris-HCl pH 8.3/75 mM KCl/3 mM MgCl₂) and 2 μl of 0.1 M DTT. The mixture was subsequently heated to 42°C for 2 min, followed by addition of 200 units of SUPERSCRIPTTM II reverse transcriptase. The reaction was carried out at 42°C for 50 min, followed by 70°C for 15 min. The first-strand cDNA was used as the template for subsequent polymerase chain reaction (PCR) amplifications.

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PCR amplification. TLR9 gene was PCR amplified from each of the above-mentioned species using primers designed from known mouse and human TLR9 sequence in Genbank: Accession AF314224 and AF259262, respectively. The primers were designed using the primer design software, Clone Manager 5 (Scientific and Educational Software, Durham, NC, USA). TLR9 gene-specific primers used were:

forward primer 5'-ACCTTGCCTGCCTTCCTACCCTGTGA-3' (SEQ ID NO:37) and reverse primer 5'-GTCCGTGTGGGCCAGCACAAA-3' (SEQ ID NO:38).

The 2.7 Kbp fragment was PCR amplified using Advantage® 2 DNA polymerase mix (BD Biosciences Clontech, Palo Alto, CA, USA) according to the manufacturer's instructions.

PCR reaction volumes of 25 μl contained 15 pmoles of each primer, 0.2 mM of dNTP mix and 1 μl of reverse transcription reaction. PCR amplification was conducted by initial denaturation at 94°C for 1 min followed by 30 cycles of 94°C denaturation (15 sec), 65°C annealing (45 sec) and 72°C extensions (2 min), with a final extension at 72°C for 5 min.

Cloning and sequencing. The PCR amplified fragment was treated with 500 units of T4 DNA polymerase (Amersham Pharmacia Biotech Inc., Baie de Urfe, Quebec) for 15 min at room temperature prior to cleaning the reaction with QIAquick PCR purification kit (QIAGEN Inc., Mississauga, ON, Canada). The fragment was then ligated to pZErOTM - 2

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vector (Invitrogen™ Life Technologies, Burlington, ON, Canada), treated with *Eco RV* restriction enzyme, using T4 DNA Ligase (GIBCO BRL®, Burlington, ON, Canada). *E. coli* TOP 10 chemically competent cells (Invitrogen™ Life Technologies, Burlington, ON, Canada) were used to transform ligated products. Plasmids containing the 2.7 Kbp fragment were sequenced using an automated DNA sequencer, CEQ™ 2000XL DNA analysis system (Beckman Coulter Inc., Fullerton, CA, USA).

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Sequences of the 2.7 Kbp fragment were derived from three clones of each species selected from independent PCR reactions to account for errors that may have been incurred during the PCR amplifications and to confirm the sequence data.

Nucleotide sequences of the rat, porcine, bovine, equine, ovine, canine, and feline TLR9 were extended and completed using standard 5' and 3' RACE PCR and primers designed using the sequences obtained from the 2.7 Kbp fragments.

Results. Nucleotide sequences of rat, porcine, bovine, equine, canine, and feline TLR9 cDNA obtained by the methods above are provided as SEQ ID NOs 3, 7, 11, 15, 19, 23, and 27, respectively. Deduced amino acid sequences are provided as SEQ ID NOs 1, 5, 9, 13, 17, 21, and 25, respectively. Deduced amino acid sequences of full-length murine and human TLR9 are provided as SEQ ID NOs 29 and 33, respectively.

Example 2. Comparison of Aligned Sequences for TLR9 from Various Mammalian Species.

Multiple sequence alignment of deduced amino acid sequences for feline, canine, bovine, mouse, ovine, porcine, horse, human, and rat TLR9 polypeptides was performed using Clustal W 1.82 (see, for example, www.cmbi.kun.nl/bioinf/tools/clustalw.shtml). In addition, paired sequence alignment of deduced amino acid sequences for murine and human TLR9 polypeptides was performed using Clustal W 1.82. The results of the multiple sequence alignment are presented in **Figure 1**. As will be appreciated from Figure 1, certain amino acids are highly conserved across all species examined. Similarly, certain amino acids differ only by conservative amino acid substitutions among the various species. In addition, it is evident that certain amino acids which are conserved between murine and human TLR9 are not conserved in other species. Furthermore, Figure 1 also indicates that certain amino acids are highly divergent across various species. The information provided by the comparison of multiple species adds significantly to the information available by comparison between only murine and human TLR9 sequences.

The putative transmembrane regions of the TLR9 polypeptides are indicated in boxes in Figure 1. Sequence upstream of each transmembrane region is extracellular domain and is believed to include sequence primarily responsible for binding to TLR9 ligands, including CpG DNA. The extracellular domains of feline, canine, bovine, mouse, ovine, porcine, horse, human, and rat TLR9 correspond to amino acids numbered 1-820, 1-822, 1-818, 1-821, 1-818, 1-819, 1-820, 1-820, and 1-821, respectively, as shown in Figure 1.

Figure 2 presents an evolutionary relatedness tree for six TLR9 polypeptides examined. The cladogram in Figure 2 was prepared using Clustal W (see above). As can be appreciated from this figure, murine and human TLR9 are nearly the most divergent TLR9s in this group. Surprisingly, human and horse TLR9 appear relatively closely related.

Example 3. Reconstitution of TLR9 Signaling in 293 Fibroblasts.

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Mouse TLR9 cDNA (SEQ ID NO:31) and human TLR9 cDNA (SEQ ID NO:35) in pT-Adv vector (from Clonetech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR9 (hTLR9) and murine TLR9 (mTLR9) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

Since NF-κB activation is central to the IL-1/TLR signal transduction pathway (Medzhitov R et al. (1998) *Mol Cell* 2:253-258; Muzio M et al. (1998) *J Exp Med* 187:2097-101), cells were transfected with hTLR9 or co-transfected with hTLR9 and an NF-κB-driven luciferase reporter construct. Human fibroblast 293 cells were transiently transfected with hTLR9 and a six-times NF-κB-luciferase reporter plasmid (NF-κB-luc) or with hTLR9 alone. After stimulus with CpG-ODN (2006, 2μM, TCGTCGTTTTGTCGTTTTGTCGTT, SEQ ID NO:58), GpC-ODN (2006-GC, 2μM, TGCTGCTTTTGTGCTTTTGTGCTT, SEQ ID NO:59), LPS (100 ng/ml) or media, NF-κB activation by luciferase readout (8h) or IL-8 production by ELISA (48h) were monitored. Results representative of three independent experiments showed that cells expressing hTLR9 responded to CpG-DNA but not to LPS.

Independently, human fibroblast 293 cells were transiently transfected with mTLR9 and the NF-κB-luc construct or with mTLR9 alone. After stimulation with CpG-ODN (1668, 2μM; TCCATGACGTTCCTGATGCT, SEQ ID NO:60), GpC-ODN (1668-GC, 2μM;

TCCATGAGCTTCCTGATGCT, SEQ ID NO:61), LPS (100 ng/ml) or media, NF-kB activation by luciferase readout (8h) or IL-8 production by ELISA (48h) were monitored. Results showed that expression of TLR9 (human or mouse) in 293 cells results in a gain of function for CpG-DNA stimulation.

To generate stable clones expressing human TLR9, murine TLR9, or either TLR9 with the NF-κB-luc reporter plasmid, 293 cells were transfected in 10 cm plates (2x10⁶ cells/plate) with 16 μg of DNA and selected with 0.7 mg/ml G418 (PAA Laboratories GmbH, Cölbe, Germany). Clones were tested for TLR9 expression by RT-PCR. The clones were also screened for IL-8 production or NF-κB-luciferase activity after stimulation with ODN. Four different types of clones were generated.

293-hTLR9-luc:

expressing human TLR9 and 6-fold NF-κB-luciferase reporter

293-mTLR9-luc:

expressing murine TLR9 and 6-fold NF-κB-luciferase reporter

293-hTLR9:

expressing human TLR9

15 293-mTLR9:

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expressing murine TLR9

Results indicated that stable clones also responded to CpG-ODN.

Example 4. Similar ODN Sequence Specificity of TLR9 of Human and Equine TLR9.

3x10⁶ 293T cells were electroporated with 5μg NF-κB-luc plasmid and 5 μg of either horse TLR9-pcDNA3.1 plasmid or humanTLR9-pcDNA3.1 plasmid at 200V, 975 μF. After the electroporation the cells were plated in 96-well cell culture plates at 2.5x10⁴ cells per well and grown overnight at 37°C. The cells were stimulated with the indicated concentration of ODN for 16h, after which the supernatant was removed and the cells lysed in lysis buffer and frozen for at least 2 hours at –80°C. Luciferase activity was measured by adding Luciferase Assay substrate from Promega. Values are given as fold specific induction over non-stimulated control. Results are shown in **Figure 3**.

As shown in Figure 3, ODN 2006 (TCGTCGTTTTGTCGTTTTGTCGTT; SEQ ID NO:58) has a strong specificity for human TLR9. ODN 1982

(TCCAGGACTTCTCAGGTT; SEQ ID NO:70) was the negative control ODN. ODN5890 (TCCATGACGTTTTTGATGTT; SEQ ID NO:39) has a strong specificity for mouse

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TLR9. This experiment demonstrates the similarity of horse TLR9 to human TLR9 in binding specificity, a result predicted by the evolutionary relatedness of horse TLR9 to human TLR9. Mouse TLR9 is more distant from horse TLR9 and human TLR9 in sequence homology, and ODN 5890 was not detected by either human or horse TLR9.

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Example 5. Non-human, Non-murine Native Mammalian TLR9 Useful in Screening for Human-Preferred CpG DNA.

Native rat, porcine, bovine, equine, and ovine TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006). Rat, porcine, bovine, equine, or ovine TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in this assay are then used as the basis for screening for additional human-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected native rat, porcine, bovine, equine, or ovine TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected native rat, porcine, bovine, equine, or ovine TLR9 polypeptide are contacted with candidate human-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA.

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Example 6. Chimeric TLR9 Useful in Screening for Human-Preferred CpG DNA.

Chimeric TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006). Chimeric TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in this assay are then used as the basis for screening for additional human-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected chimeric TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected chimeric TLR9 polypeptide are contacted with candidate human-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA.

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Example 7. Chimeric TLR9 Responsive to Both Human-Preferred and Murine-Preferred CpG DNA.

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Chimeric TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006) and also screened for binding or TLR9 signaling activity when contacted with murine-preferred CpG DNA (ODN 1668). Chimeric TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in each of these assays are then used as the basis for screening for additional human-preferred CpG DNA and for screening for additional murine-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected chimeric TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected chimeric TLR9 polypeptide are contacted with candidate human-preferred CpG DNA or candidate murine-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA. Candidate murine-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as murine-preferred CpG DNA.

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Equivalents

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages of the invention are not necessarily encompassed by each embodiment of the invention.

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All references, patents and patent publications that are recited in this application are incorporated in their entirety herein by reference.

We claim:

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Claims

- 1. An isolated polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:1, SEQ ID NO:5, SEQ ID NO:9, SEQ ID NO:13, and SEQ ID NO:17.
- 2. An isolated polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, and SEQ ID NO:18.
- 3. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:1, SEQ ID NO:5, SEQ ID NO:9, SEQ ID NO:13, and SEQ ID NO:17.
 - 4. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, and SEQ ID NO:18.
 - 5. A vector comprising the nucleic acid of any of claims 3-4.
 - 6. A cell comprising the vector of claim 5.
 - 7. An antibody or fragment thereof that binds specifically to the polypeptide of any of claims 1-2.
 - 8. A method for identifying key amino acids in a TLR9 of a first species which confer specificity for CpG DNA optimized for TLR9 of the first species, comprising:

aligning protein sequences of TLR9 of a first species, TLR9 of a second species, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for TLR9 of the first species rather than when contacted with a CpG DNA optimized for TLR9 of the second species;

generating an initial set of candidate amino acids in the TLR9 of the first species by excluding each amino acid in the TLR9 of the first species which (a) is identical with the

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TLR9 of the second species or (b) differs from the TLR9 of the second species only by conservative amino acid substitution;

generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in the TLR9 of the first species which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and

identifying as key amino acids in the TLR9 of the first species each amino acid in the refined set of candidate amino acids.

9. A method for identifying key amino acids in human TLR9 which confer specificity for CpG DNA optimized for human TLR9, comprising:

aligning protein sequences of human TLR9, murine TLR9, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for human TLR9 rather than when contacted with a CpG DNA optimized for murine TLR9;

generating an initial set of candidate amino acids in human TLR9 by excluding each amino acid in human TLR9 which (a) is identical with murine TLR9 or (b) differs from murine TLR9 only by conservative amino acid substitution;

generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in human TLR9 which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and

identifying as key amino acids in human TLR9 each amino acid in the refined set of candidate amino acids.

10. The method according to claim 9, performed iteratively with a plurality of TLR9s derived from different species other than human and mouse, wherein for each TLR9 the refined set of candidate amino acids is assigned a weight, said weight corresponding to a ratio equal to (responsiveness to human-preferred CpG DNA)/(responsiveness to murine-preferred CpG DNA).

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- 11. An isolated polypeptide comprising an amino acid sequence identical to SEQ ID NO:30 except for substitution of at least one key amino acid identifed according to the method of any of claims 9 or 10.
- 5 12. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide according to claim 11.
 - 13. A vector comprising the nucleic acid of claim 12.
- 10 14. A cell comprising the vector of claim 13.

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- 15. An antibody that binds specifically to the polypeptide of claim 14.
- 16. A screening method to identify a TLR9 ligand, comprising: contacting a polypeptide according to any of claims 1, 2, or 11 with a candidate TLR9 ligand;

measuring a signal in response to the contacting; and identifying the candidate TLR9 ligand as a TLR9 ligand when the signal in response to the contacting is consistent with TLR9 signaling.

- 17. The method of claim 16, wherein the signal comprises expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway.
- 18. The method of claim 17, wherein the reporter gene is operatively linked to a promoter sensitive to NF-κB.
 - 19. The method of claim 17, wherein the candidate TLR9 ligand is an immunostimulatory nucleic acid.
- 20. The method of claim 19, wherein the immunostimulatory nucleic acid is CpG DNA.

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21. A screening method to identify species-specific CpG-motif preference of an isolated polypeptide of claim 2 or claim 11, comprising:

contacting an isolated polypeptide of claim 2 or claim 11 with a CpG DNA comprising a hexamer sequence selected from the group consisting of GACGTT, AACGTT, CACGTT, TACGTT, GGCGTT, GCCGTT, GTCGTT, GATGTT, GAAGTT, GAGGTT, GACATT, GACCTT, GACGTT, G

measuring a signal in response to the contacting; and

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identifying a species-specific CpG-motif preference when the signal in response to the contacting is consistent with TLR9 signaling.

- 22. The method of claim 21, wherein the signal comprises expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway.
- 23. The method of claim 17, wherein the reporter gene is operatively linked to a promoter sensitive to NF-κB.
- 24. The method of claim 21, wherein the CpG DNA is an oligodeoxynucleotide having a sequence selected from the group consisting of

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TCCATGACGTTTTTGATGTT
                                    (SEQ ID NO:39),
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                                     (SEQ ID NO:40),
         TCCATAACGTTTTTGATGTT
         TCCATCACGTTTTTGATGTT
                                    (SEQ ID NO:41),
         TCCATTACGTTTTTGATGTT
                                    (SEQ ID NO:42),
         TCCATGGCGTTTTTGATGTT
                                     (SEQ ID NO:43),
                                     (SEQ ID NO:44),
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         TCCATGCCGTTTTTGATGTT
                                     (SEQ ID NO:45),
         TCCATGTCGTTTTTGATGTT
                                     (SEQ ID NO:46),
         TCCATGATGTTTTTGATGTT
                                     (SEQ ID NO:47),
         TCCATGAAGTTTTTGATGTT
                                     (SEQ ID NO:48),
         TCCATGAGGTTTTTGATGTT
         TCCATGACATTTTTGATGTT
                                     (SEO ID NO:49),
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                                     (SEQ ID NO:50),
         TCCATGACCTTTTTGATGTT
                                     (SEO ID NO:51),
         TCCATGACTTTTTTGATGTT
                                     (SEQ ID NO:52),
         TCCATGACGCTTTTGATGTT
                                     (SEO ID NO:53),
         TCCATGACGATTTTGATGTT
                                     (SEQ ID NO:54),
         TCCATGACGGTTTTGATGTT
35
                                     (SEO ID NO:55),
         TCCATGACGTCTTTGATGTT
                                     (SEQ ID NO:56), and
         TCCATGACGTATTTGATGTT
         TCCATGACGTGTTTGATGTT
                                     (SEO ID NO:57).
```

Figure 1 (1/3)

feline	MGPCHGALHPLSLLVQAAALAVALAQGTLPAFLPCELQRHGLVNCDWLFLKSVPHFSAAA	60
canine	MGPCRGALHPLSLLVQAAALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAA	60
bovine	MGP-YCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGA	50
mouse	MGP-YCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGA	59
ovine	MGP-YCAPHPLSLLVQAAALAAALAQGTLPAFLPCELQPRGKVNCNWLFLKSVPRFSAGA	59
porcine	MGP-RCTLHPLSLLVQVTALAAALAQGRLPAFLPCELQPHGLVNCNWLFLKSVPHFSAAA	59
horse	MCDCHCALODI SI LUONAMI AUNI A COMI DDEI DODI ODUCENDONO DEI CONTROLLO	59
human	MGPCHGALQPLSLLVQAAMLAVALAQGTLPPFLPCELQPHGLVNCNWLFLKSVPHFSAAA	60
rat	MGFCRSALHPLSLLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCNWLFLKSVPHFSMAA	60
rac	MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAE	60
	* : :******	
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feline	PRGNVTSLSLYSNRIHHLHDSDFVHLSSLRRLNLKWNCPPASLSPMHFPCHMTIEPHTFL	120
canine	PRGNVTSLSLYSNRIHHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFL	120
bovine	PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL	119
mouse	PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL	119
ovine	PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL	119
porcine	PRANVTSLSLLSNRIHHLHDSDFVHLSSLRTLNLKWNCPPAGLSPMHFPCHMTIEPNTFL	119
horse	PRDNVTSLSLLSNRIHHLHDSDFAQLSNLQKLNLKWNCPPAGLSPMHFPCHMTIEPNTFL	120
human	PRGNVTSLSLSSNRIHHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFL	120
rat ·	PRSNITSLSLIANRIHHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFL	120
	** *:**** :***** : **.:: :: ******* .**:*: *: ***	120
feline	AVPTLEELNLSYNSITTVPALPSSLVSLSLSRTNILVLDPANLAGLHSLRFLFLDGNCYY	100
canine	AVPTLEDLNLSYNSITTVPALPSSLVSLSLSRTNILVLDPATLAGLYALRFLFLDGNCYY	100
bovine	AVPTLEELNLSYNGITTVPALPSSLVSLSLSHTSILVLGPTHFTGLHALRFLYMDGNCYY	180
mouse	AVPILEELNLSYNGITTVPALPSSLVSLSLSHTSILVLGPTHFTGLHALRFLYMDGNCYY	1/9
ovine		
	AVPTLEELNLSYNGITTVPALPSSLVSLSLSRTSILVLGPTHFTGLHALRFLYMDGNCYY	179
porcine	AVPTLEELNLSYNSITTVPALPDSLVSLSLSRTNILVLDPTHLTGLHALRYLYMDGNCYY	
horse	AVPTLEELNLSYNGITTVPALPSSLVSLILSRTNILQLDPTSLTGLHALRFLYMDGNCYY	
human	AVPTLEELNLSYNNIMTVPALPKSLISLSLSHTNILMLDSASLAGLHALRFLFMDGNCYY	
rat	AMRMLEELNLSYNGITTVPRLPSSLTNLSLSHTNILVLDASSLAGLHSLRVLFMDGNCYY	180
	*: **:****** * *** ** .* .* .: ::**::** *::****	
feline	KNPCPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYLLLSYNHIITLAPEDL	
canine	KNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYLLLSYNHIITLAPEDL	
bovine	MNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIVTLAPEDL	
mouse	MNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIVTLAPEDL	
ovine	KNPCQQAVEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIITLAPEDL	
porcine	KNPCQGALEVVPGALLGLGNLTHLSLKYNNLTEVPRSLPPSLETLLLSYNHIVTLTPEDL	239
horse	KNPCGRALEVAPGALLGLGNLTHLSLKYNNLTTVPRSLPPSLEYLLLSYNHIVTLAPEDL	
human	KNPCRQALEVAPGALLGLGNLTHLSLKYNNLTVVPRNLPSSLEYLLLSYNRIVKLAPEDL	240
rat	KNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYLLLSYNLIVKLGAEDL	240
	*** *::*.*.*********** *** **. ***** ***	
feline	ANLTALRVLDVGGNCRRCDHARNPCMECPKGFPHLHPDTFSHLNHLEGLVLKDSSLYNLN	
canine	ANLTALRVLDVGGNCRRCDHARNPCRECPKGFPQLHPNTFGHLSHLEGLVLRDSSLYSLD	300
bovine	ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE	299
mouse	ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE	
ovine	ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE	
porcine	ANLTALRVLDVGGNCRRCDHARNPCRECPKDHPKLHSDTFSHLSRLEGLVLKDSSLYNLD	
horse	ANLTALRVLDVGGNCRRCDHARNPCVECPHKFPOLHSDTFSHLSRLEGLVLKDSSLYOLN	
human	ANLTALRVLDVGGNCRRCDHAPNPCMECPRHFPOLHPDTFSHLSRLEGLVLKDSSLSWLN	
rat	ANLTSLRMLDVGGNCRRCDHAPDLCTECROKSLDLHPOTFHHLSHLEGLVLKDSSLHSLN	
100	****:************** : * ** : . **:** **:****** *:	300
feline	PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSF	360
canine	PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSF	
bovine	KDWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSF	
mouse	KDWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSF	
ovine	KDWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTOLRRLNLSFNYHKKVSFAHLOLAPSF	
porcine	TRWFRGLDRLQVLDLSENFLYDCITKTTAFQGLARLRSLNLSFNYHKKVSFAHLHLAPSF	
horse	PRWFRGLGNLTVLDLSENFLYDCITKTKAFOGLAOLRRLNLSFNYHKKVSFAHLTLAPSF	
human	ASWFRGLGNLRVLDLSENFLYKCITKTKAFQGLTQLRKLNLSFNYQKRVSFAHLSLAPSF	
rat	SKWFQGLANLSVLDLSENFLYESINKTSAFONLTRLRKLDLSFNYCKKVSFARLHLASSF	
	: * * ***** * * * * * * * * * * * *	200
	er e e e e e e e e e e e e e e e e e e	

PCT/US2003/029577

Figure 1 (2/3)

feline	GSLLSLQQLDMHGIFFRSLSETTLRSLVHLPMLQSLHLQMNFINQAQLSIFGAFPGLRYV	420
canine	GSLLSLOELDIHGIFFRSLSKTTLOSLAHLPMLORLHLOLNFISOAQLSIFGAFPGLRYV	420
bovine	GSLVSLEKLDMHGIFFRSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFV	
mouse	GSLVSLEKLDMHGIFFRSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFV	
ovine	GGLVSLEKLDMHGIFFRSLTNTTLRPLTQLPKLQSLSLQLNFINQAELSIFGAFPSLLFV	
	GHLRSLKELDMHGIFFRSLSETTLQPLVQLPMLQTLRLQMNFINQAQLSIFGAFPGLLYV	
porcine		
horse		420
human	GSLVALKELDMHGIFFRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYV	
rat		420
	* :*::*::**** * : **: *. ** *: * **:**.**:* * .* ::	
feline	DLSDNRISGAMELAAATGEVDGGERVRLPSGDLALGPPGTPSSEGFMPGCKTLNFTLD	478
canine		480
bovine		476
	DLSDNRISGAATPAAALGEVDSRVEVWRDPRGLAPGPLDAVSSKDFMPSCN-LNFTLD	
mouse	DLSDNRISGAATPAAALGEVDSRVEVWRDPRGLAPGPLAAVSAKDFMPSCN-LNFTLD	
ovine		
porcine	DLSDNRISGAARPVAITREVDGRERVWLPSRNLAPRPLDTLRSEDFMPNCKAFSFTLD	
horse	DLSDNRISGAVEPVATTGEVDGGKKVWLTSRDLTPGPLDTPSSEDFMPSCKNLSFTLD	
human	DLSDNRISGASELTATMGEADGGEKVWLQPGDLAPAPVDTPSSEDFRPNCSTLNFTLD	
rat	DLSNNRISGPPTLSRVAPEKAD-EAEKGVPWPASLTPALPSTPVSKNFMVRCKNLRFTMD	479
	:**	
feline	LSRNNLVTIOPEMFARLSRLQCLLLSRNSISQAVNGSQFMPLTSLQVLDLSHNKLDLYHG	538
canine	LSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNLRVLDLSHNKLDLYHG	
	LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG	
bovine	LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG	536
mouse		
ovine	LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTRLRVLDLSYNKLDLYHG	
porcine	LSRNNLVTIQSEMFARLSRLECLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG	537
horse	LSRNNLVTVQPEMFAQLSRLQCLRLSHNSISQAVNGSQFVPLTSLQVLDLSHNKLDLYHG	538
human	LSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQVLDLSHNKLDLYHE	
rat	LSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLKVLDLSYNKLDLYHS	539
	**** **: *** . *: ** ** ** * * * * * * *	
feline	RSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSA	598
canine	RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA	600
bovine	RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA	596
	RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA	596
mouse	RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA	596
ovine	RSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSA	597
porcine	RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST	500
horse	RSFTELPRLEALDLS INSQFF SMRGVGHNLSF VAQUET LKILLSDARING INSQF SMRGVGHNLSF VAQUET LKILLSDARING INSGF SMRGVGHNLSF SMRGVGHNLSF VAQUET LKILLSDARING INSGF SMRGVGHNLSF S	500
human	HSFTELPRLEALDLSYNSQPFGMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST	590
rat	KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST	599
	:**:***:******************************	
feline	SLRALDFSGNALSRMWAEGDLYLHFFRGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLRLL	658
canine	SLRALDFSGNTLSOMWAEGDLYLRFFQGLRSLVQLDLSQNRLHTLLPRNLDNLPKSLRLL	660
bovine	SLRALDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQL	656
mouse	SLRALDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQL	656
ovine	SLRALDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSKNHLHTLLPRHLDNLPKSLRQL	656
	SLCALDFSGNDLSRMWAEGDLYLRFFQGLRSLVWLDLSQNHLHTLLPRALDNLPKSLKHL	657
porcine	SLWALDFSGNSLSQMWAEGDLYLRFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLL	658
horse	SLRALDFSGNALGHMWAEGDLYLHFFQGLSGLIWLDLSQNRLHTLLPQTLRNLPKSLQVL	658
human	SVEYLDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKL	650
rat	*: ***** :::** * **** **: * * * *** * * * * * * * * * * * * * * *	039
		710
feline	RLRDNYLAFFNWSSLVLLPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVAS	718
canine	RLRDNYLAFFNWSSLALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVP	120
bovine	RLRDNNLAFFNWSSLTVLPRLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIP	716
mouse	RLRDNNLAFFNWSSLTVLPRLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIP	716
ovine	RLRDNNLAFFNWSSLTVLPQLEALDLAGNQLKALSNGSLPPGTRLQKLDVSSNSIGFVTP	716
porcine	HLRDNNLAFFNWSSLTLLPKLETLDLAGNQLKALSNGSLPSGTQLRRLDLSGNSIGFVNP	717
horse	RLRNNYLAFFNWSSLTLLPNLETLDLAGNQLKALSNGSLPSGTQLQRLDVSRNSIIFVVP	718
human	RLRDNYLAFFKWWSLHFLPKLEVLDLAGNQLKALTNGSLPAGTRLRRLDVSCNSISFVAP	718
rat	SFRDNHLSFFNWSSLAFLPNLRDLDLAGNLLKALTNGTLPNGTLLQKLDVSSNSIVFVVP	719
	*** * *** * ** ** ** ** *** *** * * * *	

Figure 1 (3/3)

feline	SFFALATRLRELNLSANALKTVEPSWFGSLAGTLKVLDVTGNPLHCACGAAFVDFLLEVO	778
canine		780
bovine	-	776
mouse	GFFVRATRLIELNLSANALKTVDPSWFGSLAGTLKILDVSANPLHCACGAAFVDFLLERQ	776
ovine	GFFVLANRLKELNLSANALKTVDPFWFGRLTETLNILDVSANPLHCACGAAFVDFLLEMO	776
porcine		777
horse		
	GFFALATRLRELNLSANALRTEEPSWFGFLAGSLEVLDVSANPLHCACGAAFVDFLLQVQ	778
human		778
rat		779
	.**	
feline	AAVPGLPGHVKCGSPGQLQGRSIFAQDLRLCLDEALSWDCFGLSLLTVALGLAVPMLHHL	838
canine	AAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDEALSWVCFSLSLLAVALSLAVPMLHQL	840
bovine	EAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFGLSLLMVALGLAVPMLHHL	836
mouse	EAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFGLSLLMVALGLAVPMLHHL	836
ovine	AAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFGFSLLMVALGLAVPMLHHL	836
porcine	AAVPGLPSRVKCGSPGQLQGHSIFAQDLRLCLDETLSWNCFGISLLAMALGLVVPMLHHL	837
_		•
horse	AAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDKSLSWDCFGLSLLVVALGLAMPMLHHL	838
human	AAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFALSLLAVALGLGVPMLHHL	838
rat	TKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFGLSLLAVAVGTVLPLLQHL	839

feline	CGWDLWYCFHLCLAWLPRRGRRRGADALPYDAFVVFDKAQSAVADWVYNELRVRLEER	896
canine	CGWDLWYCFHLCLAWLPRRGRRRGVDALAYDAFVVFDKAQSSVADWVYNELRVQLEER	898
bovine	CGWDLWYCFHLCLAHLPRRRRQRGEDTLLYDAVVVFDKVQSAVADWVYNELRVQLEER	894
mouse	CGWDLWYCFHLCLAHLPRRRRORGEDTLLYDAVVVFDKVQSAVADWVYNELRVOLEER	
ovine	CGWDLWYCFHLCLAHLPRRRRQRGEDTLLYDAFVVFDKAQSAVADWYYNELRVQLEER	
porcine	CGWDLWYCFHLCLAWLPHRGORRGADALFYDAFVVFDKAQSAVADWYYNELRVQLEER	
horse	CGWDLWYCFHLGLAWLPRRGWQRGADALSYDAFVVFDKAQSAVADWYYNELRVRLEER	
	CGWDLWYCFHLCLAWLPWRGROSGRDEDALPYDAFVVFDKTQSAVADWVYNELRGQLEEC	
human	CGWDLWICFHLCLAWLFLLTRGR-RSAQALFYDAFVVFDKAQSAVADWYYNELRVRLEER	
rat	********** ** ** ** ** ** ** ** ** ** *	090
C-14	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL	056
feline		958
canine	RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL	
bovine	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL	954
mouse	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL	954
ovine		
porcine	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL	
horse	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDQVSGLLRASFLLAQQRL	
human	${\tt RGRWALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL}$	958
rat	RGRRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDKVSGLLRTSFLLAQQRL	958
	*** ****** *** *** *** *** *** *** *** *** *** ***	
feline	${\tt LEDRKDVVVLVILRPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNQ}$	1016
canine	LEDRKDVVVLVILCPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNR	1018
bovine	LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQGSFWANLGIALTRDNR	
mouse	LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQGSFWANLGIALTRDNR	1014
ovine	LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQGSFWANLGMALTRDNR	
porcine	LEDRKDVVVLVILRPDAYRSRYVRLRQRLCRQSVLLWPHQPRGQGSFWAQLGTALTRDNH	1015
horse	LEDRKDVVVLVILSPDARRSRYVRLRQRLCRQSVLFWPHQPSGQRSFWAQLGMALTRDNR	
human	LEDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH	1018
rat	LEDRKDVVVLVILRPDAHRSRYVRLRQRLCRQSVLFWPHQPNGQGSFWAQLSTALTRDNH	1018
	*********** * **************** ** *****	
feline	HFYNQNFCRGPTTAE	1031
canine	HFYNONFCRGPTTA	1032
bovine	HFYNRNFCRGPTTAE	1029
mouse	HFYNRNFCRGPTTAE	1032
ovine	HFYNRNFCRGPTTAE	1029
porcine	HFYNRNFCRGPTTAE	1030
horse	HFYNONFCRGPTMAE	1031
human	HFYNRNFCQGPTAE	1032
rat	HFYNRNFCRGPTAE	1032
	****:***	

Figure 2

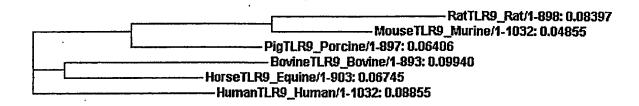
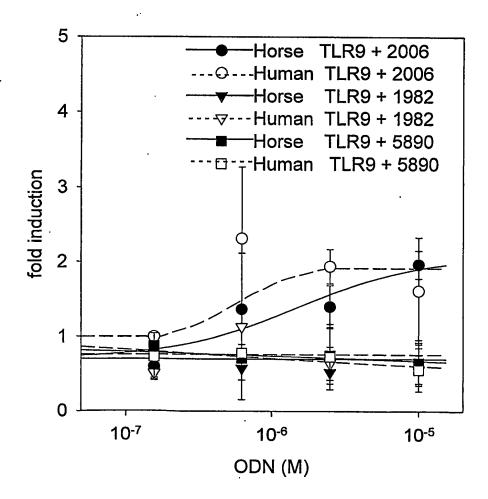


Figure 3



SEQUENCE LISTING

<110> Coley Pharmaceutical GmbH University of Saskatchewan Qiagen GmbH

<120> TOLL-LIKE RECEPTOR 9 (TLR9) FROM VARIOUS MAMMALIAN SPECIES

<130> C1041.70040WO00

<150> US 60/412,479

<151> 2002-09-19

<160> 70

<170> PatentIn version 3.1

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Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Glu Pro Arg Ser Asn 50 55 60

Ile Thr Ser Leu Ser Leu Ile Ala Asn Arg Ile His His Leu His Asn 65 70 75 80

Leu Asp Phe Val His Leu Pro Asn Val Arg Gln Leu Asn Leu Lys Trp 85 90 95

Asn Cys Pro Pro Gly Leu Ser Pro Leu His Phe Ser Cys Arg Met
100 105 110

Thr Ile Glu Pro Lys Thr Phe Leu Ala Met Arg Met Leu Glu Glu Leu
115 120 125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser 130 135 140

Leu Thr Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala 150 155 Ser Ser Leu Ala Gly Leu His Ser Leu Arg Val Leu Phe Met Asp Gly 165 170 Asn Cys Tyr Tyr Lys Asn Pro Cys Asn Gly Ala Val Asn Val Thr Pro 185 180 Asp Ala Phe Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr 200 Asn Asn Leu Thr Glu Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr 215 Leu Leu Leu Ser Tyr Asn Leu Ile Val Lys Leu Gly Ala Glu Asp Leu 230 235 Ala Asn Leu Thr Ser Leu Arg Met Leu Asp Val Gly Gly Asn Cys Arg , 245 250 Arg Cys Asp His Ala Pro Asp Leu Cys Thr Glu Cys Arg Gln Lys Ser 260 265 Leu Asp Leu His Pro Gln Thr Phe His His Leu Ser His Leu Glu Gly 275 280 Leu Val Leu Lys Asp Ser Ser Leu His Ser Leu Asn Ser Lys Trp Phe 290 295 Gln Gly Leu Ala Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu 315 Tyr Glu Ser Ile Asn Lys Thr Ser Ala Phe Gln Asn Leu Thr Arg Leu Arg Lys Leu Asp Leu Ser Phe Asn Tyr Cys Lys Lys Val Ser Phe Ala 340 345 350 Arg Leu His Leu Ala Ser Ser Phe Lys Ser Leu Val Ser Leu Gln Glu 355 360 Leu Asn Met Asn Gly Ile Phe Phe Arg Leu Leu Asn Lys Asn Thr Leu 370

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Leu Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu 690 695 700

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Phe Val Val Pro Ala 705 710 715 720

Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn 725 730 735

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Leu Pro Leu Gln His Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe 835 840 845

His Leu Cys Leu Ala Trp Leu Pro Leu Leu Thr Arg Gly Arg Arg Ser 850 855 860

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Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu 885 890 895

Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp 900 905 910

Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr 915 920 925

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Leu Phe Trp Pro His Gln Pro Asn Gly Gln Gly Ser Phe Trp Ala Gln 995 1000 1005

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- Asn Cys Pro Pro Pro Gly Leu Ser Pro Leu His Phe Ser Cys Arg Met
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Arg Cys Asp His Ala Pro Asp Leu Cys Thr Glu Cys Arg Gln Lys Ser 265 Leu Asp Leu His Pro Gln Thr Phe His His Leu Ser His Leu Glu Gly 280 Leu Val Leu Lys Asp Ser Ser Leu His Ser Leu Asn Ser Lys Trp Phe 290 295 Gln Gly Leu Ala Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu 310 Tyr Glu Ser Ile Asn Lys Thr Ser Ala Phe Gln Asn Leu Thr Arg Leu 330 Arg Lys Leu Asp Leu Ser Phe Asn Tyr Cys Lys Lys Val Ser Phe Ala 345 Arg Leu His Leu Ala Ser Ser Phe Lys Ser Leu Val Ser Leu Gln Glu 360 Leu Asn Met Asn Gly Ile Phe Phe Arg Leu Leu Asn Lys Asn Thr Leu 370 375 Arg Trp Leu Ala Gly Leu Pro Lys Leu His Thr Leu His Leu Gln Met 385 390 395 Asn Phe Ile Asn Gln Ala Gln Leu Ser Val Phe Ser Thr Phe Arg Ala 405 410 Leu Arg Phe Val Asp Leu Ser Asn Asn Arg Ile Ser Gly Pro Pro Thr 420 425

Leu Ser Arg Val Ala Pro Glu Lys Ala Asp Glu Ala Glu Lys Gly Val 435 440 445

Pro Trp Pro Ala Ser Leu Thr Pro Ala Leu Pro Ser Thr Pro Val Ser 450 455 460

Lys Asn Phe Met Val Arg Cys Lys Asn Leu Arg Phe Thr Met Asp Leu 465 470 475 480

Ser Arg Asn Asn Gln Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
485 490 495

Ser His Leu Gln Cys Leu Ser Leu Ser His Asn Cys Ile Ala Gln Ala 500 505 510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Lys Val Leu Asp 515 520 525

Leu Ser Tyr Asn Lys Leu Asp Leu Tyr His Ser Lys Ser Phe Ser Glu 530 540

Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe 545 550 555 560

Ser Met Gln Gly Ile Gly His Asn Phe Ser Phe Leu Ala Asn Leu Ser 565 570 575

Arg Leu Gln Asn Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val 580 585 590

Ser Ser Arg Leu Tyr Ser Thr Ser Val Glu Tyr Leu Asp Phe Ser Gly 595 600 605

Asn Gly Val Gly Arg Met Trp Asp Glu Glu Asp Leu Tyr Leu Tyr Phe 610 620

Phe Gln Asp Leu Arg Ser Leu Ile His Leu Asp Leu Ser Gln Asn Lys 625 630 635 640

Leu His Ile Leu Arg Pro Gln Asn Leu Asn Tyr Leu Pro Lys Ser Leu 645 650 655

Thr Lys Leu Ser Phe Arg Asp Asn His Leu Ser Phe Phe Asn Trp Ser 660 665 670

Ser Leu Ala Phe Leu Pro Asn Leu Arg Asp Leu Asp Leu Ala Gly Asn 675 680 685

Leu Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu 690 695 700

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Phe Val Val Pro Ala 705 710 715 720

Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn

725 730 735

Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
740 745 750

Leu Thr Val Leu Asp Val Ser Ser Asn Pro Leu His Cys Ala Cys Gly
755 760 765

Ala Pro Phe Val Asp Leu Leu Glu Val Gln Thr Lys Val Pro Gly
770 775 780

Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Arg Gln Leu Gln Gly Arg
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Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Asp Val Leu Ser 805 810 815

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Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Ala Asn Val 50 55 60

Thr Ser Leu Ser Leu Leu Ser Asn Arg Ile His His Leu His Asp Ser 65 70 75 80

Asp Phe Val His Leu Ser Ser Leu Arg Thr Leu Asn Leu Lys Trp Asn 85 90 95

Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys His Met Thr
100 105 110

Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn 115 120 125

Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Asp Ser Leu 130 135 140

Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro Thr 145 150 155 160

His Leu Thr Gly Leu His Ala Leu Arg Tyr Leu Tyr Met Asp Gly Asn 165 170 175

Cys Tyr Tyr Lys Asn Pro Cys Gln Gly Ala Leu Glu Val Val Pro Gly 180 185 190

Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn 195 200 205

Asn Leu Thr Glu Val Pro Arg Ser Leu Pro Pro Ser Leu Glu Thr Leu 210 215 220

Leu Leu Ser Tyr Asn His Ile Val Thr Leu Thr Pro Glu Asp Leu Ala 225 230 235 240

Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg 250 Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asp His Pro 265 Lys Leu His Ser Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu 275 280 Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asp Thr Arg Trp Phe Arg 290 295 Gly Leu Asp Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr 305 310 315 320 Asp Cys Ile Thr Lys Thr Thr Ala Phe Gln Gly Leu Ala Arg Leu Arg Ser Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His 345 Leu His Leu Ala Pro Ser Phe Gly His Leu Arg Ser Leu Lys Glu Leu 355 360 365 Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Glu Thr Thr Leu Gln 370 375 380 Pro Leu Val Gln Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met Asn 385 390 395 Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly Leu 405 410 . 415 Leu Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Arg Pro 420 425

Val Ala Ile Thr Arg Glu Val Asp Gly Arg Glu Arg Val Trp Leu Pro
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Ser Arg Asn Leu Ala Pro Arg Pro Leu Asp Thr Leu Arg Ser Glu Asp

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Phe Met Pro Asn Cys Lys Ala Phe Ser Phe Thr Leu Asp Leu Ser Arg
465 470 475 480

Asn Asn Leu Val Thr Ile Gln Ser Glu Met Phe Ala Arg Leu Ser Arg 485 490 495

Leu Glu Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn 500 505 510

Gly Ser Gln Phe Val Pro Leu Thr Ser Leu Arg Val Leu Asp Leu Ser 515 520 525

His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro 530 535 540

Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Thr Met 545 550 555 560

Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ala Leu 565 570 575

Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser Gln
580 585 590

Gln Leu Cys Ser Ala Ser Leu Cys Ala Leu Asp Phe Ser Gly Asn Asp 595 600 605

Leu Ser Arg Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg Phe Phe Gln 610 620

Gly Leu Arg Ser Leu Val Trp Leu Asp Leu Ser Gln Asn His Leu His 625 635 635

Thr Leu Leu Pro Arg Ala Leu Asp Asn Leu Pro Lys Ser Leu Lys His
645 650 655

Leu His Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu 660 665 670

Thr Leu Leu Pro Lys Leu Glu Thr Leu Asp Leu Ala Gly Asn Gln Leu 675 680 685

Lys Ala Leu Ser Asn Gly Ser Leu Pro Ser Gly Thr Gln Leu Arg Arg 690 695 700

Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Asn Pro Gly Phe Phe

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Val	Leu	Asp 755	Val	Ser	Ala	Asn	Pro 760	Leu	His	Сув	Ala	Сув 765	Gly	Ala	Thr
Phe	Val 770	Gly	Phe	Leu	Leu	Glu 775	Val	Gln	Ala	Ala	Val 780	Pro	Gly	Leu	Pro
Ser 785	Arg	Val	Lys	Cys	Gly 790	Ser	Pro	Gly	Gln	Leu 795	Gln	Gly	His	Ser	Ile 800
Phe	Ala	Gln	Asp	Leu 805	Arg	Leu	Сув	Leu	Asp 810	Glu	Thr	Leu	Ser	Trp 815	Asn
Cys	Phe	Gly	Ile 820	Ser	Leu	Leu	Ala	Met 825	Ala	Leu	Gly	Leu	Val 830	Val	Pro
Met	Leu	His 835		Leu	Cys	Gly	Trp 840	Asp	Leu	Trp	Tyr	Cys 845	Phe	His	Leu
Сув	Leu 850		Trp	Leu	Pro	His 855		Gly	Gln	Arg	Arg 860	Gly	Ala	qaA	Ala
Leu 865		Tyr	Asp	Ala	Phe 870	Val	Val	Phe	qaA	Lys 875	Ala	Gln	Ser	Ala	Val 880
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Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser Gly Leu Leu 930 935 940

Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys 945 950 955 960

Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala Tyr Arg Ser Arg 965 970 975

Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp 980 985 990

Pro His Gln Pro Arg Gly Gln Gly Ser Phe Trp Ala Gln Leu Gly Thr 995 1000 1005

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Thr Ala Leu Ala Ala Leu Ala Gln Gly Arg Leu Pro Ala Phe Leu 20 , 25 30

Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu Phe 35 40 45

Leu Lys Ser Val Pro His Phe Ser Ala Ala Pro Arg Ala Asn Val 50 55 60

Thr Ser Leu Ser Leu Leu Ser Asn Arg Ile His His Leu His Asp Ser 65 70 75 80

Asp Phe Val His Leu Ser Ser Leu Arg Thr Leu Asn Leu Lys Trp Asn 85 90 95

Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys His Met Thr 100 105 110

- 17 -

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Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Asp Ser Leu 130 135 140

Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro Thr 145 150 155 160

His Leu Thr Gly Leu His Ala Leu Arg Tyr Leu Tyr Met Asp Gly Asn 165 170 175

Cys Tyr Tyr Lys Asn Pro Cys Gln Gly Ala Leu Glu Val Val Pro Gly
180 185 190

Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn 195 200 205

Asn Leu Thr Glu Val Pro Arg Ser Leu Pro Pro Ser Leu Glu Thr Leu 210 215 220

Leu Leu Ser Tyr Asn His Ile Val Thr Leu Thr Pro Glu Asp Leu Ala 225 230 235 240

Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg 245 250 255

Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asp His Pro 260 265 270

Lys Leu His Ser Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu 275 280 285

Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asp Thr Arg Trp Phe Arg 290 295 300

Gly Leu Asp Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr 305 310 315

Asp Cys Ile Thr Lys Thr Thr Ala Phe Gln Gly Leu Ala Arg Leu Arg 325 330 335

Ser Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His 340 345 350

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Pro Leu Val Gln Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met Asn 385 390 395 400

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Gly Ser Gln Phe Val Pro Leu Thr Ser Leu Arg Val Leu Asp Leu Ser 515 520 525

His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro 530 540

Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Thr Met 545 550 555 560

Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ala Leu 565 570 575

Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser Gln 580 585 590

Gln Leu Cys Ser Ala Ser Leu Cys Ala Leu Asp Phe Ser Gly Asn Asp 595 600 605

Leu Ser Arg Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg Phe Phe Gln 610 620

Gly Leu Arg Ser Leu Val Trp Leu Asp Leu Ser Gln Asn His Leu His 625 630 635 640

Thr Leu Leu Pro Arg Ala Leu Asp Asn Leu Pro Lys Ser Leu Lys His 645 650 655

Leu His Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu 660 665 670

Thr Leu Leu Pro Lys Leu Glu Thr Leu Asp Leu Ala Gly Asn Gln Leu 675 680 685

Lys Ala Leu Ser Asn Gly Ser Leu Pro Ser Gly Thr Gln Leu Arg Arg 690 695 700

Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Asn Pro Gly Phe Phe 705 710 715 720

Ala Leu Ala Lys Gln Leu Glu Glu Leu Asn Leu Ser Ala Asn Ala Leu 725 730 735

Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Met Val Gly Asn Leu Lys 740 745 750

Val Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Thr 755 760 765

Phe Val Gly Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu Pro 770 775 780

Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly His Ser Ile 785 790 795 800

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Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser 65 70 75 80

Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn 85 90 Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys Arg Met Thr 105 Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn 120 Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser Leu 135 Val Ser Leu Ser Leu Ser His Thr Ser Ile Leu Val Leu Gly Pro Thr 150 155 His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn 165 170 Cys Tyr Tyr Met Asn Pro Cys Pro Arg Ala Leu Glu Val Ala Pro Gly 185 Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn Asn Leu Thr Glu Val Pro Arg Arg Leu Pro Pro Ser Leu Asp Thr Leu 215 Leu Leu Ser Tyr Asn His Ile Val Thr Leu Ala Pro Glu Asp Leu Ala 230 235 225 Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg 245 250 255 Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asn Phe Pro 265 , 260 Lys Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu 275 280 285

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Val Leu Lys Asp Ser Ser Leu Tyr Lys Leu Glu Lys Asp Trp Phe Arg

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Leu Tyr Asp Ala Val Val Val Phe Asp Lys Val Gln Ser Ala Val Ala 865 870 875 880

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Val Val Leu Val Ile Leu Arg Pro Ala Ala Tyr Arg Ser Arg Tyr 965 970 975

Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro 980 985 990

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Leu Lys Ser Val Pro His Phe Ser Ala Gly Ala Pro Arg Ala Asn Val 50 55 60

Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser 65 70 75 80

Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn 85 90 95

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Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn 115 120 125

Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser Leu 130 135 140

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His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn 165 170 175

Cys Tyr Tyr Met Asn Pro Cys Pro Arg Ala Leu Glu Val Ala Pro Gly 180 185 190

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Leu His Leu Ala Ser Ser Phe Gly Ser Leu Val Ser Leu Glu Lys Leu 355 360 365

Asp Met His Gly Ile Phe Phe Arg Ser Leu Thr Asn Ile Thr Leu Gln 370 380

Ser Leu Thr Arg Leu Pro Lys Leu Gln Ser Leu His Leu Gln Leu Asn 385 390 395 400

Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Ser Leu 405 410 415

Leu Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Thr Pro

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Ala Ala Leu Gly Glu Val Asp Ser Arg Val Glu Val Trp Arg Leu
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Pro Arg Gly Leu Ala Pro Gly Pro Leu Asp Ala Val Ser Ser Lys Asp 450 455 460

Phe Met Pro Ser Cys Asn Leu Asn Phe Thr Leu Asp Leu Ser Arg Asn 465 470 475 480

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Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn Gly
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Ser Gln Phe Val Pro Leu Thr Ser Leu Arg Val Leu Asp Leu Ser His 515 520 525

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Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln 545 550 555 560

Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ser Leu Arg 565 570 575

Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser Gln Lys
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Leu Ser Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn Ser Leu 595 600 605

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<212> PRT

<213> Equus caballus

<400> 13

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Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu 35 40 . 45

Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Asp Asn 50 55 60

Val Thr Ser Leu Ser Leu Leu Ser Asn Arg Ile His His Leu His Asp 65 70 75 80

Ser Asp Phe Ala Gln Leu Ser Asn Leu Gln Lys Leu Asn Leu Lys Trp 85 90 95

Asn Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys His Met 100 105 110

Thr Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu 115 120 125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser 130 135 140

Leu Val Ser Leu Ile Leu Ser Arg Thr Asn Ile Leu Gln Leu Asp Pro 145 150 . 155 160

Thr Ser Leu Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly 165 170 175

- Asn Cys Tyr Tyr Lys Asn Pro Cys Gly Arg Ala Leu Glu Val Ala Pro 180 185 190
- Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205
- Asn Asn Leu Thr Thr Val Pro Arg Ser Leu Pro Pro Ser Leu Glu Tyr 210 215 220
- Leu Leu Ser Tyr Asn His Ile Val Thr Leu Ala Pro Glu Asp Leu 225 230 235 240
- Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg 245 250 255
- Arg Cys Asp His Ala Arg Asn Pro Cys Val Glu Cys Pro His Lys Phe 260 265 270
- Pro Gln Leu His Ser Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly 275 280 285
- Leu Val Leu Lys Asp Ser Ser Leu Tyr Gln Leu Asn Pro Arg Trp Phe 290 295 300
- Arg Gly Leu Gly Asn Leu Thr Val Leu Asp Leu Ser Glu Asn Phe Leu 305 310 315 320
- Tyr Asp Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Ala Gln Leu 325 330 335
- Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala 340 345 350
- His Leu Thr Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu 355 360 365
- Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Gln Lys Thr Leu 370 380
- Gln Pro Leu Ala Arg Leu Pro Met Leu Gln Arg Leu Tyr Leu Gln Met 385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Lys Asp Phe Pro Gly Leu Arg Tyr Ile Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Val Glu Pro Val Ala Thr Thr Gly Glu Val Asp Gly Gly Lys Lys Val Trp Leu Thr Ser Arg Asp Leu Thr Pro Gly Pro Leu Asp Thr Pro Ser Ser Glu Asp Phe Met Pro Ser Cys Lys Asn Leu Ser Phe Thr Leu Asp Leu Ser Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser Arg Leu Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn Gly Ser Gln Phe Val Pro Leu Thr Ser Leu Gln Val Leu Asp Leu Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Arg Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Thr Leu Arg Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser Gln Gln Leu Cys Ser Thr Ser Leu Trp Ala Leu Asp Phe Ser Gly Asn Ser Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg Phe Phe Gln Gly Leu Arg Ser Leu Ile Arg Leu Asp Leu Ser Gln Asn Arg Leu

His Thr Leu Leu Pro Cys Thr Leu Gly Asn Leu Pro Lys Ser Leu Gln 645 650 655

- Leu Leu Arg Leu Arg Asn Asn Tyr Leu Ala Phe Phe Asn Trp Ser Ser 660 665 670
- Leu Thr Leu Leu Pro Asn Leu Glu Thr Leu Asp Leu Ala Gly Asn Gln 675 680 685
- Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Ser Gly Thr Gln Leu Gln 690 695 700
- Arg Leu Asp Val Ser Arg Asn Ser Ile Ile Phe Val Val Pro Gly Phe 705 710 715 720
- Phe Ala Leu Ala Thr Arg Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala 725 730 735
- Leu Arg Thr Glu Glu Pro Ser Trp Phe Gly Phe Leu Ala Gly Ser Leu 740 745 750
- Glu Val Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala 755 760 765
- Ala Phe Val Asp Phe Leu Leu Gln Val Gln Ala Ala Val Pro Gly Leu 770 780
- Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser 785 790 795 800
- Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Lys Ser Leu Ser Trp 805 810 815
- Asp Cys Phe Gly Leu Ser Leu Leu Val Val Ala Leu Gly Leu Ala Met 820 825 830
- Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His 835 840 845
- Leu Gly Leu Ala Trp Leu Pro Arg Arg Gly Trp Gln Arg Gly Ala Asp 850 855 860
- Ala Leu Ser Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala

865 870 875 880

Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu Glu Arg 885 890 895

Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu
900 905 910

Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser 915 920 925

Arg Lys Met Leu Phe Val Leu Ala His Thr Asp Gln Val Ser Gly Leu 930 935 940

Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg 945 950 955 960

Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Ala Arg Arg Ser 965 970 975

Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Phe 980 985 990

Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln Leu Gly
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<212> PRT

<213> Equus caballus

<400> 14

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Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu

35 40 45

Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Asp Asn 50 55 60

Val Thr Ser Leu Ser Leu Leu Ser Asn Arg Ile His His Leu His Asp 65 70 75 80

Ser Asp Phe Ala Gln Leu Ser Asn Leu Gln Lys Leu Asn Leu Lys Trp 85 90 95

Asn Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys His Met 100 105 110

Thr Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu 115 120 125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser 130 135 140

Leu Val Ser Leu Ile Leu Ser Arg Thr Asn Ile Leu Gln Leu Asp Pro 145 150 155 160

Thr Ser Leu Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly
165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Gly Arg Ala Leu Glu Val Ala Pro 180 185 190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205

Asn Asn Leu Thr Thr Val Pro Arg Ser Leu Pro Pro Ser Leu Glu Tyr 210 215 220

Leu Leu Ser Tyr Asn His Ile Val Thr Leu Ala Pro Glu Asp Leu 225 230 235 240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg 245 250 255

Arg Cys Asp His Ala Arg Asn Pro Cys Val Glu Cys Pro His Lys Phe 260 265 270

Pro Gln Leu His Ser Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly 275 280 285

Leu Val Leu Lys Asp Ser Ser Leu Tyr Gln Leu Asn Pro Arg Trp Phe 290 295 300

Arg Gly Leu Gly Asn Leu Thr Val Leu Asp Leu Ser Glu Asn Phe Leu 305 310 315 320

Tyr Asp Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Ala Gln Leu 325 330 335

Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala 340 345 350

His Leu Thr Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu 355 360 365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Gln Lys Thr Leu 370 375 380

Gln Pro Leu Ala Arg Leu Pro Met Leu Gln Arg Leu Tyr Leu Gln Met 385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Lys Asp Phe Pro Gly 405 410 415

Leu Arg Tyr Ile Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Val Glu 420 425 430

Pro Val Ala Thr Thr Gly Glu Val Asp Gly Gly Lys Lys Val Trp Leu 435 440 445

Thr Ser Arg Asp Leu Thr Pro Gly Pro Leu Asp Thr Pro Ser Ser Glu 450 455 460

Asp Phe Met Pro Ser Cys Lys Asn Leu Ser Phe Thr Leu Asp Leu Ser 465 470 475 480

Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser 485 490 495

Arg Leu Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val 500 505 510

- 42 -

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Leu Arg Thr Glu Glu Pro Ser Trp Phe Gly Phe Leu Ala Gly Ser Leu

Glu Val Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
755 760 765

Ala Phe Val Asp Phe Leu Leu Gln Val Gln Ala Ala Val Pro Gly Leu 770 780

Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser 785 790 795 800

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Asp Cys Phe Gly 820

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<213> Equus caballus

<400> 15

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<211> 2460

<212> DNA

<213> Equus caballus

<400> 16

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Pro Cys Glu Leu Gln Pro Arg Gly Lys Val Asn Cys Asn Trp Leu Phe 35 40 45

Leu Lys Ser Val Pro Arg Phe Ser Ala Gly Ala Pro Arg Ala Asn Val 50 55 60

Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser 65 70 75 80

Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn 85 90 95

Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys Arg Met Thr
100 105 110

Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn 115 120 125

Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser Leu 130 135 140

Val Ser Leu Ser Leu Ser Arg Thr Ser Ile Leu Val Leu Gly Pro Thr 145 150 155 160

His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn 165 170 175

Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Val Glu Val Ala Pro Gly 180 185 190

Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn 195 200 205

Asn Leu Thr Glu Val Pro Arg Arg Leu Pro Pro Ser Leu Asp Thr Leu 210 215 220

Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asn Phe Pro Lys Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu Val Leu Lys Asp Ser Ser Leu Tyr Lys Leu Glu Lys Asp Trp Phe Arg Gly Leu Gly Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr Asp Tyr Ile Thr Lys Thr Thr Ile Phe Arg Asn Leu Thr Gln Leu Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His Leu Gln Leu Ala Pro Ser Phe Gly Gly Leu Val Ser Leu Glu Lys Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Thr Asn Thr Thr Leu Arg Pro Leu Thr Gln Leu Pro Lys Leu Gln Ser Leu Ser Leu Gln Leu Asn Phe Ile Asn Gln Ala Glu Leu Ser Ile Phe Gly Ala Phe Pro Ser Leu Leu Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Arg Pro Val Ala Ala Leu Gly Glu Val Asp Ser Gly Val Glu Val Trp Arg Trp Pro Arg Gly Leu Ala Pro Gly Pro Leu Ala Ala Val Ser Ala Lys Asp

Phe Met Pro Ser Cys Asn Leu Asn Phe Thr Leu Asp Leu Ser Arg Asn Asn Leu Val Thr Ile Gln Gln Glu Met Phe Thr Arg Leu Ser Arg Leu Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn Gly Ser Gln Phe Val Pro Leu Thr Arg Leu Arg Val Leu Asp Leu Ser Tyr Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Gln Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ser Leu Arg Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser Gln Lys Leu Ser Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn Ser Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Cys Phe Phe Lys Gly Leu Arg Asn Leu Val Gln Leu Asp Leu Ser Lys Asn His Leu His Thr Leu Leu Pro Arg His Leu Asp Asn Leu Pro Lys Ser Leu Arg Gln Leu Arg Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu Thr Val Leu Pro Gln Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln Leu Lys

Ala Leu Ser Asn Gly Ser Leu Pro Pro Gly Thr Arg Leu Gln Lys Leu 690 695 700

Asp Val Ser Ser Asn Ser Ile Gly Phe Val Thr Pro Gly Phe Phe Val 705 710 715 720

Leu Ala Asn Arg Leu Lys Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys
725 730 735

Thr Val Asp Pro Phe Trp Phe Gly Arg Leu Thr Glu Thr Leu Asn Ile 740 745 750

Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Ala Phe 755 760 765

Val Asp Phe Leu Leu Glu Met Gln Ala Ala Val Pro Gly Leu Ser Arg 770 775 780

Arg Val Thr Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser Ile Phe 785 790 795 800

Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Thr Leu Ser Leu Asp Cys 805 810 815

Phe Gly Phe Ser Leu Leu Met Val Ala Leu Gly Leu Ala Val Pro Met 820 825 830

Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His Leu Cys 835 840 845

Leu Ala His Leu Pro Arg Arg Arg Gln Arg Gly Glu Asp Thr Leu 850 855 860

Leu Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala Val Ala 865 870 875 880

Asp Trp Val Tyr Asn Glu Leu Arg Val Gln Leu Glu Glu Arg Arg Gly 885 890 895

Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu Pro Gly 900 905 910

Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser Arg Lys 915 920 925

Thr Met Phe Val Leu Asp His Thr Asp Arg Val Ser Gly Leu Leu Arg

930 935 940

Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys Asp 945 950 955 960

Val Val Leu Val Ile Leu Arg Pro Ala Ala Tyr Arg Ser Arg Tyr 965 970 975

Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro 980 985 990

His Gln Pro Ser Gly Gln Gly Ser Phe Trp Ala Asn Leu Gly Met Ala 995 1000 1005

Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Arg Asn Phe Cys Arg 1010 1015 1020

Gly Pro Thr Thr Ala Glu 1025

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<213> Ovis aries

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Met Gly Pro Tyr Cys Ala Pro His Pro Leu Ser Leu Leu Val Gln Ala 1 5 10 15

Ala Ala Leu Ala Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe Leu 20 25 30

Pro Cys Glu Leu Gln Pro Arg Gly Lys Val Asn Cys Asn Trp Leu Phe 35 40 45

Leu Lys Ser Val Pro Arg Phe Ser Ala Gly Ala Pro Arg Ala Asn Val 50 55 60

Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser 65 70 75 80

Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn 85 90 95

Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys Arg Met Thr

100 105 ' 110

Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn 115 120 125

Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser Leu 130 135 140

Val Ser Leu Ser Leu Ser Arg Thr Ser Ile Leu Val Leu Gly Pro Thr 145 150 155 160

His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn 165 170 175

Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Val Glu Val Ala Pro Gly
180 185 190

Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn 195 200 205

Asn Leu Thr Glu Val Pro Arg Arg Leu Pro Pro Ser Leu Asp Thr Leu 210 215 220

Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu Ala 225 230 235 240

Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg 245 250 255

Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asn Phe Pro 260 265 270

Lys Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu 275 280 285

Val Leu Lys Asp Ser Ser Leu Tyr Lys Leu Glu Lys Asp Trp Phe Arg 290 295 300

Gly Leu Gly Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr 305 310 315 320

Asp Tyr Ile Thr Lys Thr Thr Ile Phe Arg Asn Leu Thr Gln Leu Arg 325 330 335

Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His 340 345 350

Leu Gln Leu Ala Pro Ser Phe Gly Gly Leu Val Ser Leu Glu Lys Leu 355 360 365

Asp Met His Gly Ile Phe Phe Arg Ser Leu Thr Asn Thr Thr Leu Arg 370 375 380

Pro Leu Thr Gln Leu Pro Lys Leu Gln Ser Leu Ser Leu Gln Leu Asn 385 390 395 400

Phe Ile Asn Gln Ala Glu Leu Ser Ile Phe Gly Ala Phe Pro Ser Leu 405 410 415

Leu Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Arg Pro 420 425 430

Val Ala Ala Leu Gly Glu Val Asp Ser Gly Val Glu Val Trp Arg Trp
435 440 445

Pro Arg Gly Leu Ala Pro Gly Pro Leu Ala Ala Val Ser Ala Lys Asp 450 455 460

Phe Met Pro Ser Cys Asn Leu Asn Phe Thr Leu Asp Leu Ser Arg Asn 465 470 475 480

Asn Leu Val Thr Ile Gln Gln Glu Met Phe Thr Arg Leu Ser Arg Leu 485 490 495

Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn Gly 500 505 510

Ser Gln Phe Val Pro Leu Thr Arg Leu Arg Val Leu Asp Leu Ser Tyr 515 520 525

Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Gln 530 540

Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln 545 550 555 560

Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ser Leu Arg 565 570 575

- 54 -

Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser Gln Lys
580 585 590

Leu Ser Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn Ser Leu 595 600 605

Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Cys Phe Phe Lys Gly 610 620

Leu Arg Asn Leu Val Gln Leu Asp Leu Ser Lys Asn His Leu His Thr 625 630 635 640

Leu Leu Pro Arg His Leu Asp Asn Leu Pro Lys Ser Leu Arg Gln Leu 645 650 655

Arg Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu Thr 660 665 670

Val Leu Pro Gln Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln Leu Lys 675 680 685

Ala Leu Ser Asn Gly Ser Leu Pro Pro Gly Thr Arg Leu Gln Lys Leu 690 695 700

Asp Val Ser Ser Asn Ser Ile Gly Phe Val Thr Pro Gly Phe Phe Val 705 710 715 720

Leu Ala Asn Arg Leu Lys Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys
725 730 735

Thr Val Asp Pro Phe Trp Phe Gly Arg Leu Thr Glu Thr Leu Asn Ile 740 745 750

Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Ala Phe 755 760 765

Val Asp Phe Leu Leu Glu Met Gln Ala Ala Val Pro Gly Leu Ser Arg 770 775 780

Arg Val Thr Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser Ile Phe 785 790 795 800

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3199

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<213> Ovis aries

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<213> Canis familiaris

<400> 21

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Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu 35 40 45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Pro Arg Gly Asn 50 55 60

Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp 65 70 75 80

Tyr Asp Phe Val His Phe Val His Leu Arg Arg Leu Asn Leu Lys Trp 85 90 95

Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met
100 105 110

Thr Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Asp Leu 115 120 125

Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser 130 135 140

Leu Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro 145 150 155 160

Ala Thr Leu Ala Gly Leu Tyr Ala Leu Arg Phe Leu Phe Leu Asp Gly 165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Leu Gln Val Ala Pro 180 185 190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205

Asn Asn Leu Thr Val Val Pro Arg Gly Leu Pro Pro Ser Leu Glu Tyr 210 215 220

Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu 225 230 235 240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg 245 250 255

Arg Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Gly Phe 260 265 270

Pro Gln Leu His Pro Asn Thr Phe Gly His Leu Ser His Leu Glu Gly 275 280 285

Leu Val Leu Arg Asp Ser Ser Leu Tyr Ser Leu Asp Pro Arg Trp Phe 290 295 300

His Gly Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu 305 310 315 320

Tyr Asp Cys Ile Thr Lys Thr Lys Ala Phe Tyr Gly Leu Ala Arg Leu 325 330 335

Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala 340 345 350

His Leu His Leu Ala Ser Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu 355 360 365

Leu Asp Ile His Gly Ile Phe Phe Arg Ser Leu Ser Lys Thr Thr Leu 370 375 380

Gln Ser Leu Ala His Leu Pro Met Leu Gln Arg Leu His Leu Gln Leu 385 390 395 400

Asn Phe Ile Ser Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly 405 410 415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Glu 420 425 430

Pro Ala Ala Ala Thr Gly Glu Val Glu Ala Asp Cys Gly Glu Arg Val 435 440 445

Trp Pro Gln Ser Arg Asp Leu Ala Leu Gly Pro Leu Gly Thr Pro Gly 450 455 460

Ser Glu Ala Phe Met Pro Ser Cys Arg Thr Leu Asn Phe Thr Leu Asp 465 470 475 480

Leu Ser Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Val Arg
485 490 495

Leu Ala Arg Leu Gln Cys Leu Gly Leu Ser His Asn Ser Ile Ser Gln 500 505 510

Ala Val Asn Gly Ser Gln Phe Val Pro Leu Ser Asn Leu Arg Val Leu 515 520 525

Asp Leu Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr 530 535 540

Glu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro

545 550 · 555 560

Phe Ser Met Arg Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu 565 570 575

Pro Ala Leu Arg Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg 580 585 590

Val Ser Gln Gln Leu Arg Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser 595 600 605

Gly Asn Thr Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg 610 620

Phe Phe Gln Gly Leu Arg Ser Leu Val Gln Leu Asp Leu Ser Gln Asn 625 630 635 640

Arg Leu His Thr Leu Leu Pro Arg Asn Leu Asp Asn Leu Pro Lys Ser 645 650 655

Leu Arg Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp 660 665 670

Ser Ser Leu Ala Leu Leu Pro Lys Leu Glu Ala Leu Asp Leu Ala Gly 675 680 685

Asn Gln Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln 690 695 700

Leu Gln Arg Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Val Pro
705 710 715 720

Ser Phe Phe Ala Leu Ala Val Arg Leu Arg Glu Leu Asn Leu Ser Ala 725 730 735

Asn Ala Leu Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Leu Ala Gly 740 745 750

Ala Leu Lys Val Leu Asp Val Thr Ala Asn Pro Leu His Cys Ala Cys 755 760 765

Gly Ala Thr Phe Val Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro 770 775 780

Gly Leu Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly 785 790 795 800

- Arg Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu 805 810 815
- Ser Trp Val Cys Phe Ser Leu Ser Leu Leu Ala Val Ala Leu Ser Leu 820 825 830
- Ala Val Pro Met Leu His Gln Leu Cys Gly Trp Asp Leu Trp Tyr Cys 835 840 845
- Phe His Leu Cys Leu Ala Trp Leu Pro Arg Arg Gly Arg Arg Arg Gly 850 855 860
- Val Asp Ala Leu Ala Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln 865 870 875 880
- Ser Ser Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Gln Leu Glu 885 890 895
- Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp 900 905 910
- Trp Val Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr 915 920 925
- Ser Ser Arg Lys Thr Leu Phe Val Leu Ala Arg Thr Asp Arg Val Ser 930 935 940
- Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu 945 950 955 960
- Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Cys Pro Asp Ala His 965 970 975
- Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val 980 985 990
- Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln 995 1000 1005
- Leu Gly Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln 1010 1015 1020

Asn Phe Cys Arg Gly Pro Thr Thr Ala 1025 1030

<210> 22

<211> 822

<212> PRT

<213> Canis familiaris

<400> 22

Met Gly Pro Cys Arg Gly Ala Leu His Pro Leu Ser Leu Leu Val Gln 1 5 10 15

Ala Ala Leu Ala Leu Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe
20 25 30

Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu 35 40 45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Pro Arg Gly Asn 50 55 60

Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp 65 70 75 80

Tyr Asp Phe Val His Phe Val His Leu Arg Arg Leu Asn Leu Lys Trp 85 90 95

Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met 100 105 110

Thr Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Asp Leu 115 120 125

Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser 130 135 140

Leu Val Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro 145 150 155 160

Ala Thr Leu Ala Gly Leu Tyr Ala Leu Arg Phe Leu Phe Leu Asp Gly
165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Leu Gln Val Ala Pro 180 185 190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn Asn Leu Thr Val Val Pro Arg Gly Leu Pro Pro Ser Leu Glu Tyr Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Gly Phe Pro Gln Leu His Pro Asn Thr Phe Gly His Leu Ser His Leu Glu Gly Leu Val Leu Arg Asp Ser Ser Leu Tyr Ser Leu Asp Pro Arg Trp Phe His Gly Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr Asp Cys Ile Thr Lys Thr Lys Ala Phe Tyr Gly Leu Ala Arg Leu Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His Leu His Leu Ala Ser Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu Leu Asp Ile His Gly Ile Phe Phe Arg Ser Leu Ser Lys Thr Thr Leu Gln Ser Leu Ala His Leu Pro Met Leu Gln Arg Leu His Leu Gln Leu Asn Phe Ile Ser Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Glu

Pro Ala Ala Thr Gly Glu Val Glu Ala Asp Cys Gly Glu Arg Val
435 440 445

Trp Pro Gln Ser Arg Asp Leu Ala Leu Gly Pro Leu Gly Thr Pro Gly 450 455 460

Ser Glu Ala Phe Met Pro Ser Cys Arg Thr Leu Asn Phe Thr Leu Asp 465 470 475 480

Leu Ser Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Val Arg 485 490 495

Leu Ala Arg Leu Gln Cys Leu Gly Leu Ser His Asn Ser Ile Ser Gln 500 505 510

Ala Val Asn Gly Ser Gln Phe Val Pro Leu Ser Asn Leu Arg Val Leu 515 520 525

Asp Leu Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr 530 540

Glu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro 545 550 555 560

Phe Ser Met Arg Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu 565 570 575

Pro Ala Leu Arg Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg 580 585 590

Val Ser Gln Gln Leu Arg Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser 595 600 605

Gly Asn Thr Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg 610 620

Phe Phe Gln Gly Leu Arg Ser Leu Val Gln Leu Asp Leu Ser Gln Asn 625 635 640

Arg Leu His Thr Leu Leu Pro Arg Asn Leu Asp Asn Leu Pro Lys Ser 645 650 655

Leu Arg Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp

660 665 670

Ser Ser Leu Ala Leu Leu Pro Lys Leu Glu Ala Leu Asp Leu Ala Gly 675 680 685

Asn Gln Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln 690 695 700

Leu Gln Arg Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Val Pro 705 710 715 720

Ser Phe Phe Ala Leu Ala Val Arg Leu Arg Glu Leu Asn Leu Ser Ala 725 730 735

Asn Ala Leu Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Leu Ala Gly 740 745 750

Ala Leu Lys Val Leu Asp Val Thr Ala Asn Pro Leu His Cys Ala Cys 755 760 765

Gly Ala Thr Phe Val Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro 770 780

Gly Leu Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly
785 790 795 800

Arg Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu 805 810 815

Ser Trp Val Cys Phe Ser 820

<210> 23

<211> 3334

<212> DNA

<213> Canis familiaris

<400> 23

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<210> 24

<400> 24

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<211> 2466

<212> DNA

<213> Canis familiaris

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	ttcagc						2466

<210> 25

<211> 1031

<212> PRT

<213> Felis catus

<400> 25

Met Gly Pro Cys His Gly Ala Leu His Pro Leu Ser Leu Leu Val Gln 1 5 10 15

Ala Ala Ala Leu Ala Val Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe 20 25 30

Leu Pro Cys Glu Leu Gln Arg His Gly Leu Val Asn Cys Asp Trp Leu 35 40 45

Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Gly Asn 50 55 60

Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp 65 70 75 80

Ser Asp Phe Val His Leu Ser Ser Leu Arg Arg Leu Asn Leu Lys Trp 85 90 95

Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met 100 105 110

Thr Ile Glu Pro His Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu 115 120 125

Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser 130 140

Leu Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro 145 150 155 160

- Ala Asn Leu Ala Gly Leu His Ser Leu Arg Phe Leu Phe Leu Asp Gly 165 170 175
- Asn Cys Tyr Tyr Lys Asn Pro Cys Pro Gln Ala Leu Gln Val Ala Pro 180 185 190
- Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205
- Asn Asn Leu Thr Ala Val Pro Arg Gly Leu Pro Pro Ser Leu Glu Tyr 210 215 220
- Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu 225 230 235 240
- Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg 245 250 255
- Arg Cys Asp His Ala Arg Asn Pro Cys Met Glu Cys Pro Lys Gly Phe 260 265 270
- Pro His Leu His Pro Asp Thr Phe Ser His Leu Asn His Leu Glu Gly 275 280 285
- Leu Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asn Pro Arg Trp Phe 290 295 300
- His Ala Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu 305 310 315 320
- Tyr Asp Cys Ile Thr Lys Thr Thr Ala Phe Gln Gly Leu Ala Gln Leu 325 330 335
- Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala 340 345 350
- His Leu His Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Gln 355 360 365
- Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Glu Thr Thr Leu 370 375 380

Arg Ser Leu Val His Leu Pro Met Leu Gln Ser Leu His Leu Gln Met Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Met Glu Leu Ala Ala Ala Thr Gly Glu Val Asp Gly Gly Glu Arq Val Arq Leu Pro Ser Gly Asp Leu Ala Leu Gly Pro Pro Gly Thr Pro Ser Ser Glu Gly Phe Met Pro Gly Cys Lys Thr Leu Asn Phe Thr Leu Asp Leu Ser Arg Asn Asn Leu Val Thr Ile Gln Pro Glu Met Phe Ala Arg Leu Ser Arg Leu Gln Cys Leu Leu Ser Arg Asn Ser Ile Ser Gln Ala Val Asn Gly Ser Gln Phe Met Pro Leu Thr Ser Leu Gln Val Leu Asp Leu Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ala Leu Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser Gln Gln Leu Cys Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn

Ala Leu Ser Arg Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe

610 620

Arg Gly Leu Arg Ser Leu Val Arg Leu Asp Leu Ser Gln Asn Arg Leu 625 630 635 640

His Thr Leu Leu Pro Arg Thr Leu Asp Asn Leu Pro Lys Ser Leu Arg 645 650 655

Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp Ser Ser 660 665 670

Leu Val Leu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln 675 680 685

Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln Leu Gln 690 695 700

Arg Leu Asp Leu Ser Ser Asn Ser Ile Ser Phe Val Ala Ser Ser Phe 705 710 715 720

Phe Ala Leu Ala Thr Arg Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
725 730 735

Leu Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Leu Ala Gly Thr Leu 740 745 750

Lys Val Leu Asp Val Thr Gly Asn Pro Leu His Cys Ala Cys Gly Ala 755 760 765

Ala Phe Val Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu 770 775 780

Pro Gly His Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser 785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp 805 810 815

Asp Cys Phe Gly Leu Ser Leu Leu Thr Val Ala Leu Gly Leu Ala Val 820 825 830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His 835 840 845

Leu Cys Leu Ala Trp Leu Pro Arg Arg Gly Arg Arg Gly Ala Asp 850 855 860

Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala 865 870 875 888

Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu Glu Arg 885 890 895

Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu 900 905 910

Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser 915 920 925

Arg Lys Met Leu Phe Val Leu Ala His Thr Asp Arg Val Ser Gly Leu 930 935 940

Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg 945 950 955 960

Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His Arg Ser 965 970 975

Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu 980 985 990

Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln Leu Gly 995 1000 1005

Thr Ala Leu Thr Arg Asp Asn Gln His Phe Tyr Asn Gln Asn Phe 1010 1015 1020

Cys Arg Gly Pro Thr Thr Ala Glu 1025 1030

<210> 26

<211> 820

<212> PRT

<213> Felis catus

<400> 26

Met Gly Pro Cys His Gly Ala Leu His Pro Leu Ser Leu Leu Val Gln 1 5 10 15

Ala Ala Ala Leu Ala Val Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe 20 25 30

- Leu Pro Cys Glu Leu Gln Arg His Gly Leu Val Asn Cys Asp Trp Leu 35 40 45
- Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Gly Asn 50 55 60
- Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp 65 70 75 80
- Ser Asp Phe Val His Leu Ser Ser Leu Arg Arg Leu Asn Leu Lys Trp 85 90 95
- Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met 100 105 110
- Thr Ile Glu Pro His Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu 115 120 125
- Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser 130 135 140
- Leu Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro 145 150 155 160
- Ala Asn Leu Ala Gly Leu His Ser Leu Arg Phe Leu Phe Leu Asp Gly 165 170 175
- Asn Cys Tyr Tyr Lys Asn Pro Cys Pro Gln Ala Leu Gln Val Ala Pro 180 185 190
- Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205
- Asn Asn Leu Thr Ala Val Pro Arg Gly Leu Pro Pro Ser Leu Glu Tyr 210 215 220
- Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu 225 230 235 240
- Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
 245 250 255

Arg Cys Asp His Ala Arg Asn Pro Cys Met Glu Cys Pro Lys Gly Phe 260 265 270

Pro His Leu His Pro Asp Thr Phe Ser His Leu Asn His Leu Glu Gly 275 280 285

Leu Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asn Pro Arg Trp Phe 290 295 300

His Ala Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu 305 310 315

Tyr Asp Cys Ile Thr Lys Thr Thr Ala Phe Gln Gly Leu Ala Gln Leu 325 330 335

Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala 340 345 350

His Leu His Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Gln 355 360 365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Glu Thr Thr Leu 370 375 380

Arg Ser Leu Val His Leu Pro Met Leu Gln Ser Leu His Leu Gln Met 385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly 405 410 415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Met Glu
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Leu Ala Ala Ala Thr Gly Glu Val Asp Gly Glu Arg Val Arg Leu
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Pro Ser Gly Asp Leu Ala Leu Gly Pro Pro Gly Thr Pro Ser Ser Glu 450 455 460

Gly Phe Met Pro Gly Cys Lys Thr Leu Asn Phe Thr Leu Asp Leu Ser 465 470 475 480

Arg Asn Asn Leu Val Thr Ile Gln Pro Glu Met Phe Ala Arg Leu Ser 485 490 495

Arg Leu Gln Cys Leu Leu Ser Arg Asn Ser Ile Ser Gln Ala Val Asn Gly Ser Gln Phe Met Pro Leu Thr Ser Leu Gln Val Leu Asp Leu Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ala Leu Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser Gln Gln Leu Cys Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn Ala Leu Ser Arg Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe Arg Gly Leu Arg Ser Leu Val Arg Leu Asp Leu Ser Gln Asn Arg Leu His Thr Leu Leu Pro Arg Thr Leu Asp Asn Leu Pro Lys Ser Leu Arg Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp Ser Ser Leu Val Leu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln Leu Gln Arg Leu Asp Leu Ser Ser Asn Ser Ile Ser Phe Val Ala Ser Ser Phe Phe Ala Leu Ala Thr Arg Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala

725 730 735

Leu Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Leu Ala Gly Thr Leu 740 745 750

Lys Val Leu Asp Val Thr Gly Asn Pro Leu His Cys Ala Cys Gly Ala 755 760 765

Ala Phe Val Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu 770 780

Pro Gly His Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser 785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp 805 810 815

Asp Cys Phe Gly 820

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Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu 35 40 45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn 50 55 60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn 65 70 75 80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp 85 90 95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met 100 105 110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu 115 120 125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser 130 135 140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala 145 150 155 160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly 165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro 180 185 190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr 210 215 220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu

225					230					235					240
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Arg	Сув	Asp	His 260	Ala	Pro	Asn	Pro	Сув 265	Ile	Glu	Сув	Gly	Gln 270	Lys	Ser
Leu	His	Leu 275	His	Pro	Glu	Thr	Phe 280	His	His	Leu	Ser	His 285	Leu	Glu	Gly
Leu	Val 290	Leu	Lys	Asp	Ser	Ser 295	Leu	His	Thr	Leu	Asn 300	Ser	Ser	Trp	Phe
Gln 305	Gly	Leu	Val	Asn	Leu 310	Ser	Val	Leu	Asp	Leu 315	Ser	Glu	Asn	Phe	Leu 320
Tyr	Glu	Ser	Ile	Asn 325	His	Thr	Asn	Ala	Phe 330	Gln	Asn	Leu	Thr	Arg 335	Leu
Arg	Lys	Leu	Asn 340	Leu	Ser	Phe	Asn	Tyr 345	Arg	Lys	ГХв	Val	Ser 350	Phe	Ala
Arg	Leu	His 355	Leu	Ala	Ser	Ser	Phe 360	Lys	Asn	Leu	Val	Ser 365	Leu	Gln	Glu
Leu	Asn 370	Met	Asn	Gly	Ile	Phe 375	Phe	Arg	Ser	Leu	Asn 380	Lys	Tyr	Thr	Leu
Arg 385	Trp	Leu	Ala	Asp	Leu 390	Pro	Ьув	Leu	His	Thr 395	Leu	His	Leu	Gln	Met 400
Asn	Phe	Ile	Asn	Gln 405	Ala	Gln	Leu	Ser	Ile 410	Phe	Gly	Thr	Phe	Arg 415	Ala
Leu	Arg	Phe	Val 420	Asp	Leu	Ser	Asp	Asn 425	Arg	Ile	Ser	Gly	Pro 430	Ser	Thr
Leu	Ser	Glu 435	Ala	Thr	Pro	Glu	Glu 440	Ala	Asp	Asp	Ala	Glu 445	Gln	Glu	Glu
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Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn Ile Leu Lys Thr Val Asp Arq Ser Trp Phe Gly Pro Ile Val Met Asn Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly Ala Ala Phe Val Asp Leu Leu Glu Val Gln Thr Lys Val Pro Gly Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser Trp Asp Cys Phe Gly Leu Ser Leu Leu Ala Val Ala Val Gly Met Val Val Pro Ile Leu His His Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe His Leu Cys Leu Ala Trp Leu Pro Leu Leu Ala Arg Ser Arg Arg Ser Ala Gln Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser

Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu 945 950 955 960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His 965 970 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val 980 985 990

Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln 995 1000 1005

Leu Ser Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln 1010 1015 1020

Asn Phe Cys Arg Gly Pro Thr Ala Glu 1025 1030

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Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn 50 55 60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn 65 70 75 80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp 85 90 95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met 100 105 110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu 115 120 125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser 130 135 140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala 145 150 155 160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly 165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro 180 185 190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr 210 215 220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu 225 230 235 240

Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg 245 250 255

Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser 260 265 270

Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly
275 280 285

Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe 290 295 300

Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu 305 310 315 320

Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu 325 330 335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala

340 345 350

Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu 355' 360 365

Leu Asn Met Asn Gly Ile Phe Phe Arg Ser Leu Asn Lys Tyr Thr Leu 370 380

Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met 385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala 405 410 415

Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr 420 425 430

Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Glu Glu 435 440 445

Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser 450 455 460

Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu 465 470 475 480

Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu 485 490 495

Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala 500 505 510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp 515 520 525

Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu 530 540

Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe 545 550 555 560

Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Ala His Leu Ser 565 570 575

Met Leu His Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val 580 585 590

- Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly 595 600 605
- Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe 610 620
- Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn 625 630 630 635
- Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu
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- Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr 660 665 670
- Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn 675 680 685
- Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu 690 695 700
- Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala 705 710 715 720
- Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn 725 730 735
- Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn 740 745 750
- Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly 755 760 765
- Ala Ala Phe Val Asp Leu Leu Glu Val Gln Thr Lys Val Pro Gly
 770 780
- Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg
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- Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser 805 810 815

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<213> Mus musculus

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<213> Homo sapiens

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Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu 35 40 45

Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn 50 55 60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp 65 70 75 80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp 85 90 95

- Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met 100 105 110
- Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu 115 120 125
- Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser 130 135 140
- Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser 145 150 155 160
- Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly 165 170 175
- Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro 180 185 190
- Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205
- Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr 210 215 220
- Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu 225 230 235 240
- Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
 245 250 255
- Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe 260 265 270
- Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly 275 280 285
- Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe 290 295 300
- Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu

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Arg	Lys	Leu	Asn 340	Leu	Ser	Phe	Asn	Tyr 345	Gln	Lys	Arg	Val	Ser 350	Phe	Ala
His	Leu	Ser 355	Leu	Ala	Pro	Ser	Phe 360	Gly	Ser	Ļeu	Val	Ala 365	Leu	Lys	Glu
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Leu	Arg	Tyr	Val 420	Asp	Leu	Ser	Asp	Asn 425	Arg	Ile	Ser	Gly	Ala 430	Ser	Glu
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Gln	Pro 450	Gly	Asp	Leu	Ala	Pro 455	Ala	Pro	Val	Asp	Thr 460	Pro	Ser	Ser	Glu
Asp 465	Phe	Arg	Pro	Asn	Cys 470	Ser	Thr	Leu	Asn	Phe 475	Thr	Leu	Asp	Leu	Ser 480
Arg	Asn	Asn	Leu	Val 485	Thr	Val	Gln	Pro	Glu 490	Met	Phe	Ala	Gln	Leu 495	Ser
His	Leu	Gln	Сув 500	Leu	Arg	Leu	Ser	His 505	Asn	Cys	Ile	Ser	Gln 510	Ala	Val
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Ser	Arg 530	Asn	Lys	Leu	Asp	Leu 535	Tyr	His	Glu	His	Ser 540	Phe	Thr	Glu	Leu

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Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly 545 550 555 560

- Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr 565 570 575
- Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser 580 585 590
- Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn 595 600 605
- Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe 610 620
- Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu 625 630 635 640
- His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln 645 650 655
- Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser 660 665 670
- Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg 675 680 685
- Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg 690 695 700
- Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe 705 710 715 720
- Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala 725 730 735
- Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu 740 745 750
- Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
 755 760 765
- Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu 770 780

Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser 785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp 805 810 815

Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val 820 825 830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His 835 840 845

Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp 850 855 860

Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln 865 870 875 880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu 885 890 895

Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp 900 905 910

Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr 915 920 925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser 930 935 940

Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu 945 950 955 960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg 965 970 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val 980 985 990

Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln 995 1000 1005

Leu Gly Met Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg 1010 1015 1020

Asn Phe Cys Gln Gly Pro Thr Ala Glu 1025 1030

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<212> PRT

<213> Homo sapiens

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Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu 35 40 45

Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn 50 55 60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp 65 70 75 80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp 85 90 95

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met 100 105 110

Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu 115 . 120 125 .

Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser 130 135 140

Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser 145 150 155 160

Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly 165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro 180 185 190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205

Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr 210 215 220

Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu 225 230 235 240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
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Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe 260 265 270

Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly 275 280 285

Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe 290 295 300

Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu 305 310 315 320

Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu 325 330 335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala 340 345 350

His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu 355 360 365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu 370 380

Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met 385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly
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Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu

420 425 430

Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Glu Lys Val Trp Leu 435 440 445

Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu 450 455 460

Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser 465 470 475 480

Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser 485 490 495

His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val 500 505 510

Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu 515 520 525

Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu 530 535 540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly 545 550 555 560

Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr 565 570 575

Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser 580 585 590

Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn 595 600 605

Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe 610 625 620

Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu 625 630 635

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